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TISSUE OXYGEN TENSION OF CERVIX CANCER

Comparison of effects of breathing a carbon dioxide mixture and pure oxygen

by

PER BERGSJØ and JOHN C EVANS

The influence of varied inspired oxygen on malignant tissue radiosensitivity has been the subject of considerable research speculation and clinical investigation in numerous radiotherapy centers It is quite well documented that many types of human cancer tend to outgrow their blood supply with consequent development of areas of hypoxic but viable cancer cells These would presumably be less radiosensitive than the well oxygenated surrounding normal tissues Attempts have been made to alter this situation by administration of 100 % oxygen prior to irradiation at atmospheric or elevated pressure Since the use of oxygen under high pressure is more time consuming and hazardous to the patient we have chosen to investigate the use of oxygen at atmospheric pressure in patients with carcinoma of the cervix The present study was designed to determine the influence of adding carbon dioxide to the inspired oxygen on

From the Gynecologic Department (Director Oddmund Koller) of the Norwegian Radium Hospital (Director Reidar Eker) Montebello Oslo Norway The investigation was in part supported by a Public Health Service Fellowship (No 1—F3—CA—19 559—01 to J C E) from the National Cancer Inst U S Public Health P B was a Fellow of the Norwegian Cancer Society Submitted for publication 16 February 1967

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tissue oxygen tension in the cervix cancers as determined by polarographic measurement

Several investigators have compared the use of a mixture of 5 % CO_2 and 95 % O_2 to 100 % O_2 during irradiation of animal tumors In experiments with spontaneous mammary adenocarcinomas in mice, DuSault (1963) found a higher cure rate following fractionated radiation treatment with the animals on a mixture of 5 % CO_2 and 95 % O_2 than with 100 % O_2 The proportion of mice with impalpable tumor two months after irradiation was nearly as great after treatment with this mixture at atmospheric pressure as with oxygen at three atmospheres Inch, McCredie & Kruuv (1966) treated two types of mammary carcinomas in mice, an 'isotransplant' which had been carried serially for many generations in C_3H mice, and an 'isoimplant' from a spontaneous C_3H mammary tumor to first and second generation offspring of the same strain Only in the latter did the 5 % CO_2 mixture give a 'cure rate' (impalpable at 100 days) greater than 100 % oxygen

Assuming that these results could be explained through an increase in tumor blood circulation, a search for a possible CO_2 effect on the oxygen tension of human cancers seemed indicated We have examined the oxygen tension in cancer of the uterine cervix by polarography in a large series of patients, and have continuously recorded changes in pO_2 with the patients breathing pure oxygen at one atmosphere's pressure In an unselected group of these patients we have compared the effects of breathing 100 % O_2 with those of breathing a mixture of 5 % CO_2 and 95 % O_2

Material and Methods

The *material* comprised 37 patients with carcinoma of the uterine cervix in clinical stage II (36 had squamous cell carcinoma, and one had an adenocarcinoma) Some of the patients were examined two or three times during the early phase of external irradiation, resulting in 55 different examinations

The comparisons to be analyzed were carried out both before and during radiation treatment As radiation induced changes in the tumor tissue could possibly influence the oxygen and carbon dioxide responses, the conditions at the time of the examinations are described, and the results analyzed separately

Treatment commenced for all the patients with a series of 12 betatron fractions to external pelvic fields, and during this period the present investigation included three special examinations Irradiations from 31 and 33 MeV betatrons were used, 200 R (Victoreen) skin dose per fraction, each fraction being delivered in about 10 minutes Five to six fractions were given per week

The first examination was made before treatment, the second examination



Fig 1 Electrode in position in tumor tissue Colpophotograph according to the method of KOLLER (1964) × 10

after 775 R (Victoreen) delivered in 5 fractions and 6 days the third examination after 1 700 R (Victoreen) delivered in 11 fractions and 15 days These average doses have been bas d upon the isodose charts and a mean estimated tumor depth

The *oxygen tension* was measured directly in tumor tissue by means of bare platinum micro-electrodes of 2̣0 μ diameter (The electrodes were kindly furnished by Mr Paul V Gabel of the Albert Einstein College of Medicine New York N Y U S A)

The electrodes were placed superficially in the tumors guided by a Zeiss colposcope at 10 to 15 times magnification (Fig 1) This enabled the examiner to see blood vessels down to capillary size distinctly and choose an avascular area between vessels for placement of the electrodes As previously described the distance between these superficial capillaries in cervix cancer is often greater than 350 μ (KOLSTAD 1964) The chance of hitting blood vessels below the tumor surface was diminished by the very superficial position of the electrodes Active bleeding was seldom observed either at the time of insertion or during the recording when the electrodes were controlled regularly by inspection

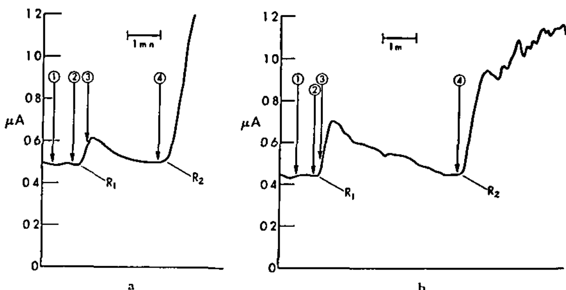


Fig 2 Determination of response times by continuous recording of the polarographic current. The symbols indicate 1—the patient breathes air 2—inhalation of 5 % CO_2 and 95 % O_2 starts R_1—initial deflection from the control level distance between 2 and R_1=response time 3—air breathing is resumed and when the original air breathing level has been reached at 4—100 % O is administered R_2—new point of deflection from control level

a) Code No 50 first examination In this case both response times were equal each measuring 9 seconds

b) Code No 51 second examination The response time for the CO_2 mixture was 12 seconds and for the 100 % O it was 9 seconds

The vagina was kept open by a self retracting Cusco speculum, and the electrodes were kept in position in the tumor during the whole examination A Polariter PO4 (Radiometer, Copenhagen) was used for recording the polarographic current and the silver coated Cusco speculum was utilized as reference electrode By a sweeping voltage curve with the electrode in tissue, a plateau was noted to occur between — 0 3 and — 0 6 volts The comparisons of maximum oxygen tensions were made with a fixed voltage of — 0 4 V Since bare platinum electrodes cannot be calibrated in absolute units of oxygen tension, change in tissue pO_2 are reported in units of microamperes (μ A)

Experimental procedure A platinum electrode was inserted in the tumor tissue and polarized until a steady state current had been recorded The gases to be compared, 100 % O and the mixture of 5 % CO and 95 % O_2, were then administered alternately at atmospheric pressure through an ordinary anesthesia face mask A Ruben valve prevented rebreathing of expired air The patient was instructed, and the mask was applied tightly to the face

The special examinations were time consuming, often lasting up to three

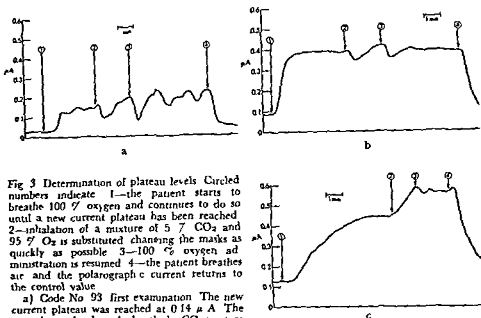


Fig 3 Determination of plateau levels Circled numbers indicate 1—the patient starts to breathe 100 % oxygen and continues to do so until a new current plateau has been reached 2—inhalation of a mixture of 5 % CO_2 and 95 % O_2 is substituted changing the masks as quickly as possible 3—100 % oxygen administration is resumed 4—the patient breathes air and the polarographic current returns to the control value

a) Code No 93 first examination The new current plateau was reached at 0 14 μ A The new plateau level reached with the CO_2 mixture was 0 20 μ A the rise after resuming oxygen breathing may represent a residual effect of the CO_2. The curve demonstrates a CO_2 effect by the rapid increase in pO_2 from the plateau level during oxygen administration

b) Code No 96 third examination. After radiation therapy the plateau levels of the polarographic current on air and oxygen breathing were higher than at the first examination A brief administration of the 5 % CO_2 mixture (at 2) resulted in a slight increase in pO_2 from 0 38 μ A to 0 41 μ A which is not a significant change

c) Code No 85 third examination After administration of oxygen there was again a high plateau current (0 44 μ A) An increase to 0 56 μ A followed the period of breathing the 5 % CO_2 mixture This is the maximal difference observed after radiation therapy and suggests a CO_2 effect.

quarters of an hour (colpophotography generally preceding the pO measurements) The patients were very cooperative but not to tire them unnecessarily certain time limits were observed Further we did not want the patients to experience any untoward effects of carbon dioxide breathing and therefore made them breathe the CO_2 mixture for only a few minutes at a time This determined the sequence of gas breathing to be found in the examples of records and the tables of results Concern for the patients precluded an ideal experimental set up

Two parameters were compared response time and plateau level

Response time is the time (in seconds) from mask application to the first detectable deviation of the recorded polarographic current from the control value The initial deflection from the control level was generally quite distinct and to ensure reproducible conditions the mask was always applied immediately prior

to inspiration. If the response to both O_2 and the CO_2—O_2 mixture was ill defined, the records were omitted from comparison. The response time thus represents the lung uterus circulation time plus the intratumor circulation and diffusion time.

Plateau level represents the maximum increase in current following the first five to ten minutes of oxygen breathing.

All comparisons have been paired, meaning that each patient breathed both gases alternately during the same examination, under essentially the same conditions. The second response time was determined only after the control value of polarographic current, on room air, had been reached. For plateau levels, the masks with different gases were changed as quickly as possible to make the 'dip' in pO_2 as small as possible. The sequence of events is illustrated in the examples of Figs. 2 and 3.

Wilcoxon's test for pair differences was used, the probabilities relating to the two-tailed test (Documenta Geigy Scientific Tables 1962).

Results

Response time. Comparisons of response time at the first, second and third examinations are shown in Tables 1, 2 and 3, respectively. No difference was found in any of the groups between the response time of the two gases. If all the response times are compared without relation to treatment, there is still no difference between the gases, suggesting that any small difference between the individual examinations most likely has been due to chance.

Plateau level. Comparisons of the first and third examinations are shown in Tables 4 and 5. Before radiation treatment the tumor oxygen tension attained a higher plateau when the CO_2 mixture was administered to the patient than when pure oxygen was given.

The difference found for the first examination could not be confirmed for the third. It should be noted, however, that the plateau levels on oxygen found at the third examinations were generally much higher than those at the first.

In the comparisons of Tables 4 and 5, the CO_2 mixture was administered after the pure oxygen. In a number of patients, oxygen was administered a second time after the few minutes of the CO_2 mixture, with no difference observed in the plateau response.

Discussion

Our results indicate that the inhalation of a mixture of 5 % CO_2 and 95 % O_2 may result in slightly higher tumor oxygen tension in cervix cancer before radiation treatment than the inhalation of 100 % O_2 at one atmosphere's

Tables 1 to 3

Comparison of response times at the 1st 2nd and 3rd examinations — Horizontally the response times are arranged in true examination order vertically the arrangement is according to Wilcoxon's test for paired comparisons — CO_2 indicates the 5 carbon dioxide mixture and O_2 the pure oxygen

Code number	Response time in seconds (in order of application)			Wilcoxon's test between CO_2 first and O_2 second		
	CO_2	O_2	CO_2	Diff	Rank number	
Table 1 — First examination						
50	9	9	—	0		
56	21	21	—	0		
43	15	17	—	2	1	
B-a	12	9	—	3		2
B-b	18	21	15	3	3	
57	6	9	—	3	4	
41	24	21	21	3		5
53	45	39	—	6		6
42	33	42	15	9	7	
52	0	15	—	15	8	
				T = 13 n = 8 2α > 10 No difference		
Table 2 — Second examination						
38		51	33			
48	—	15	18			
39	15	15	—	0		
51	12	9	—	3		1
43	18	12	12	6		2
44	18	12	—	6		3
40	21	10	10	11		4
52	14	0	—	14		5
				T_s = 15 n = 5 2α = 10 Series too small for conclusion		
Table 3 — Third examination						
38	15	15		0		
39	24	24		0		
52	18	18		0		
42	27	30		3	1	
35	15	10		5		2
43	30	36		6	3	
40	18	12		6		4
48	3	9		6	5	
47	21	30		9	6	
				T = 6 n = 6 2α > 10 No difference		

Tables 4 and 5

Comparisons of plateau levels — Arrangement as for tables 1 to 3

Code number	Baseline current (air breathing) $\mu A \times 100$	Plateau level $\mu A \times 100$: 100 % O_2	Plateau level $\mu A \times 100$: 5 % CO_2 95 % O_2	Plateau level increase over baseline in %: 100 % O_2	Plateau level increase over baseline in %: 5 % CO_2 95 % O_2	Wilcoxon's test: % Diff	Wilcoxon's test: Rank number	
Table 4 — First examination								
90	14	19	19	136	136	0		
105	10	18	17	180	170	10		1
94	3	23	22	760	733	38		2.5
111	3	4	5	133	166	33	2.5	
110	5	13	15	260	300	40	4	
104	1	3	4	300	400	100	5	
101	1	11	13	1 100	1 300	200	6	
103	1	25	27	2 500	2 700	200	7	
93	3	14	20	467	667	200	8	
96	1	13	17	1 300	1 700	100	9	
						T_s = 3.5 n = 9 .05 > 2α > .02 Significant difference		
Table 5 — Third examination (after irradiation)								
84	20	44	43	220	215	5		1
83	7	11	12	157	172	15	2	
89	6	16	18	267	300	33	3	
96	9	38	41	422	456	34	4	
87	20	67	76	335	380	45	5	
86	13	39	32	300	246	54		6
88	11	22	15	200	136	64		7
90	14	36	45	257	322	65	8	
94	11	54	45	491	409	82		9
85	13	44	56	338	432	94	10	
						T_s = 23 n = 10 2α > .10 No difference		

pressure. Since the inspired gas contained 5 % by volume less oxygen, the opposite effect could be expected if the hypercapnia was without effect. This effect of CO_2 on tumor oxygen tension could not be observed during radiation treatment. No difference was found in the response time between the two gases.

Carbon dioxide acts as a respiratory stimulant. The effect on the circulation

is complex There is increased cardiac output The direct effect on blood vessels is dilatation whereas the indirect effect is activation of the sympathetic nervous system Peripherally local vasodilatation appears to be stronger than the nervous vasoconstriction (GOODMAN & GILMAN 1965) There is evidence that carbon dioxide also acts directly upon tumor vessels of transplantable mouse hepatomas (KLIGERMAN & HENEL 1961) but the response is unpredictable Another factor to consider is that carbon dioxide produces a shift to the right in the oxyhemoglobin dissociation curve, the most important result probably being a b tter oxygen yield to the tissues

These considerations suggest that CO might increase oxygen tension in peripheral tissues and possibly also in tumors Increased tumor oxygen tension is also the most likely explanation of the better results of radiotherapy in animals reported by DUSAULT (1963) and by INCH MCCREDIE & KRUUV (1966) The latter investigators noted an effect in poorly vascularized *isoimplants but not in* well vascularized isotransplants

Our results may be of some help in differentiating the mechanisms whereby hypercapnea might increase tumor oxygen Since the measurement of lung tumor circulation time indicated by the response time, remains unchanged, increased cardiac output does not seem to be a significant mechanism Peripheral vasodilatation might give a real increase in tissue oxygen tension or an *apparent in*crease due to lessened distance from the measuring electrode *to the capillary wall* An increase in the plateau reading of pO *with the CO* mixture was observed only in the unirradiated cancers This suggests that if the tumor vessels are *already* maximally dilated by the radiation effect similar to the radiation *erythema of skin* there will be no response to other vasodilating agents The higher plateau level of tumor pO on oxygen *after radiation* therapy would support this assumption A similar rise in average pO in tumor following external radiation therapy has been observed with *the* patient breathing air in a much larger series of cas s (to be published elsewhere) *Since* the plateau reading is higher after radiation both with air and oxygen breathing a vasodilating effect of CO may be present but *more difficult* to demonstrate and possibly of less significance A ri e in pO *due to a shift* in the oxyhemoglobin dissociation curve would not be *expected to* show any relation to radiation treatment and may b assumed to be of less importance

Since the CO mixture was administered after O_2 a conditioning effect of pure O cannot be ruled out As *previously* stated oxygen was administered a second time after the few *minutes of the* CO mixture in several patients, with no difference observed in the *plateau response* To really test this possibility however would have required more *prolonged* administration of the CO mixture before O which was not done because *of concern for* the patients

Tables 4 and 5

Comparisons of plateau levels — Arrangement as for tables 1 to 3

Code number	Baseline current (air breathing) μA×100	Plateau level μA×100		Plateau level increase over baseline in %		Wilcoxon s test		
		100 % O_2	5 % CO_2 95 % O_2	100 % O_2	5 % CO_2 95 % O_2	% Diff	Rank number	
Table 4 — First examination								
90	14	19	19	136	136	0		
105	10	18	17	180	170	10		1
94	3	23	22	766	733	38		2 5
111	3	4	5	133	166	33	2 5	
110	5	13	15	260	300	40	4	
104	1	3	4	300	400	100	5	
101	1	11	13	1 100	1 300	200	6	
103	1	25	27	2 500	2 700	200	7	
93	3	14	20	467	667	200	8	
96	1	13	17	1 300	1 700	400	9	
						$T_1 = 3$ 5 n = 9 05 > 2α > 02 Significant difference		
Table 5 — Third examination (after irradiation)								
84	20	44	43	220	215	5		1
83	7	11	12	157	172	15	2	
89	6	16	18	267	300	33	3	
96	9	38	41	422	456	34	4	
87	20	67	76	335	380	45	5	
86	13	39	32	300	246	54		6
88	11	22	15	200	136	64		7
90	14	36	45	257	322	65	8	
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85	13	44	56	338	432	94	10	
						T = 23 n − 10 2α 10 No difference		

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Carbon dioxide acts as a respiratory stimulant The effect on the circulation

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Previous studies of cervix cancer have demonstrated that hypoxic foci are probably present (KOLSTAD 1964). Since the range of low pO_2 which causes reduced radiosensitivity but not cell death is very limited, any slight increase in tumor pO_2 may theoretically be of importance (DESCHNER & GRAY 1959). Whether this can be achieved by administration of 100 % O_2 at atmospheric pressure is presently being tested in a clinical trial at the Norwegian Radium Hospital. The present study suggests that a mixture of 5 % CO_2 and 95 % O_2 may give better tumor oxygenation than pure oxygen, if administered at the beginning of radiotherapy.

SUMMARY

Clinical tests were made in 37 patients with carcinoma of the uterine cervix to investigate the effect on tumor oxygen tension of a mixture containing 5 % CO_2 and 95 % O_2 as compared to the effect of 100 % O_2 inhaled at one atmosphere's pressure. Oxygen tension was measured polarographically in tumor tissue. Before the radiation treatment, the CO_2 mixture resulted in slightly higher maximum oxygen tension than the breathing of pure O_2. After a series of fractionated external betatron treatments this difference had disappeared, which would seem to indicate that the observed increase in tumor oxygen tension associated with the addition of CO_2 be due primarily to vasodilatation of tumor vessels.

ZUSAMMENFASSUNG

Klinische Versuche wurden an 37 Patientinnen mit Karzinom des Cervix uteri vorgenommen, um die Wirkung am Sauerstoffdruck des Tumorgewebes von einer Mischung enthaltend 5 % CO_2 und 95 % O_2 im Vergleich mit der Wirkung von 100 % O_2 inhaliert beim Druck von 1 Atmosphäre zu untersuchen. Der Sauerstoffdruck wurde polarographisch im Tumorgewebe gemessen. Bevor der Bestrahlungstherapie bewirkte die CO_2-Mischung einen unbedeutend höheren maximalen Sauerstoffdruck als die Inhalation von reinem Sauerstoff. Nach einer Reihe von externen Betatronbestrahlungen verschwand dieser Unterschied, was vermuten liess, dass die mit der Zugabe von CO_2 beobachtete Zunahme im Tumor-Sauerstoffdruck vor allem der Dilatation der Blutgefässe des Tumors zuzuschreiben sei.

RÉSUMÉ

Des tests cliniques ont été pratiqués sur 37 malades atteintes de cancer du col de l'utérus pour comparer les effets sur la tension d'oxygène de la tumeur d'un mélange contenant 5 % de CO_2 et 95 % d'O_2 et les effets de l'oxygène pur inhalé à la pression d'une atmosphère. La tension d'oxygène a été mesurée polarographiquement dans le tissu tumoral. Avant le traitement par les radiations, le mélange contenant du CO_2 donnait des tensions maximales d'oxygène un peu supérieures à celles que donnait l'inhalation d'oxygène pur. Après une série de traitements externes fractionnés par le bétatron, cette différence disparait, ce qui fait penser que l'augmentation de la tension d'oxygène de la tumeur liée à l'addition de CO_2 soit due essentiellement à la dilatation des vaisseaux de la tumeur.

flammation as a result REFVEM (1954) believed the lesions to be of the same type as in other granulomatous inflammatory conditions and to be caused by a protein complex, forming on reaction between tumour antigen and phospholipid rich antibodies

A fair proportion of the published cases of epithelioid cell granulomatosis in the region of malignant growths have been seen in patients irradiated for carcinoma of the uterine cervix Radiotherapy has often been related to the development of epithelioid cell granulomatosis because radiation certainly accelerates the destruction of the tumour tissue with consequent increase in the frequency of the lesions The most likely explanation for the relatively high frequency of cervical carcinoma in these series is perhaps that squamous epithelial growths are more prone to cause epithelioid cell granulomatosis than others

This investigation is a continuation of the work of GORTON & LINELL in Lund upon epithelioid cell granulomatosis and was carried out to determine whether any variation in frequency occurred with age lymph node metastases or tumour stage or with the intensity and duration of the radiotherapy given

Material and Methods The material consisted of 145 patients with carcinoma of the uterine cervix examined between 1958 and 1964 and operated upon ad *modum* Wertheim with regional lymphadenectomy One hundred and thirty nine of these patients had squamous epithelial carcinoma and 6 had adenocarcinoma Four of the patients had not undergone radiotherapy

The patients mostly received preoperative roentgen therapy (four pelvic fields of 1 200 to 2 400 R per field) and intra uterovaginal radium treatment (three treatments at 10 day intervals with a total dose of 6 800 to 7 200 mg/hr for 3 to 4 weeks) The interval between termination of radiotherapy and operation was at least 2 months and seldom more than 3 months

Results

Eight of the 145 patients (5 5 %) were found to have epithelioid cell granulomatosis of the regional lymph nodes Two of them had both epithelioid cell granulomatosis and metastases In none of these eight patients had preoperative roentgen examination revealed any obvious change Preoperative examination of seven of the patients had included serum electrophoresis The α_1 α_2 and γ values were moderately increased in six including one patient with palpable axillary lymph nodes and one with palpable inguinal lymph nodes No biopsy specimens of these lesions were obtained Urography disclosed no signs of tuberculosis or other abnormalities in any of the eight patients

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SARCOID-LIKE LESIONS (EPITHELIOID CELL GRANULOMATOSIS) OF REGIONAL LYMPH NODES IN ASSOCIATION WITH CARCINOMA OF THE CERVIX

by

BENGT HOGSTEDT

The occurrence of sarcoid like lesions in the regional lymph nodes in patients with various forms of malignant epithelial tumours was first described in the beginning of the 1950s (GHERARDI 1950, NADEL & ACKERMANN 1950, SYMMERS 1951 and GORTON 1953) Larger series have since been reported (GORTON & LINELL 1957 with 34 cases, WUKETICH 1959 with 29 cases, and HAGERSTRAND & LINELL 1964 with 14 autopsy cases) Thirty two cases in all have also been described by TEN SELDAM (1956), DONATI et coll (1961) and *CHIECO BIANCHI (1963)*

Epithelioid cell granulomatosis of the regional lymph nodes has also been seen in association with other types of neoplasms Thus, GORTON & LINELL reported one case of sarcoma of the uterus and one of malignant melanoma and WUKETICH one case of seminoma

According to most authors, the lesions should be distinguished from generalized sarcoidosis The changes are believed to be due to a local reaction of the lymph nodes to disintegrating tumour tissue with granulomatous in

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that in the present series epithelioid cell granulomatosis was diagnosed only once between the years 1961 to 1964. Since sarcoid lesions are sometimes transient and may be related to radiotherapy, the patients with epithelioid cell granulomatosis were studied for any difference from the rest of the series regarding the interval between the beginning of radiotherapy and the time of the operation. No such difference was however apparent and the interval did not vary from year to year either. The moderate variation of the duration of radiotherapy (see the table) may be explained by the somewhat longer treatment in stages II—IV.

The interval in the series of GORTON & LINELL between termination of radiotherapy and the operation was usually 4 months, compared with 2 to 3 months in the present series. This difference can however hardly explain the decrease during the years from 1961 to 1964, for the treatment was the same throughout the entire 1958—1964 period.

No differences with respect to age, stage of tumour or metastases to the lymph nodes could be found between patients with and, respectively, without epithelioid cell granulomatosis.

SUMMARY

Eight out of a series of 145 women operated upon for carcinoma of the uterine cervix were found to have developed epithelioid cell granulomatosis of the regional lymph nodes.

ZUSAMMENFASSUNG

Es fand sich, dass in acht von 145 Frauen, die für Cervixkarzinom operiert worden waren, eine Epitheloidzellengranulomatose der Regionallymphdrüsen vorlag.

RÉSUMÉ

Sur une série de 145 femmes opérées pour cancer du col de l'utérus, huit présentaient une granulomatose à cellules épithéloïdes des ganglions lymphatiques de la région.

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Table

Survey of the material — 145 patients with carcinoma of the uterine cervix examined between 1958 and 1964

	Number of patients	With epithelioid granulomatosis	Mean age	Tumour stages			Spread to lymph nodes	Duration of preoperative radiotherapy in days		
				I	II	III—IV		Stage I	Stages II-IV	Total
1958	31	2	45.0	21	4	2	3	100	115	103
1959	23	4	43.5	13	10	0	4	105	111	108
1960	23	1	47.9	13	8	2	3	108	119	113
1961	23	0	42.7	12	9	2	3	104	118	111
1962	16	0	42.9	10	6	0	8	115	113	114
1963	12	0	51.4	8	4	0	4	126	139	130
1964	17	1	45.3	8	8	1	2	105	100	102
Total	145	8	45.2	89	49	7	27	106	115	110

Three of the patients with epithelioid cell granulomatosis have in the meantime died from recurrence of tumour and have been examined post mortem. The deaths occurred 2, 3 and 6 years after operation. No sarcoid lesions were evident in the organs examined histologically (lungs, heart, liver, spleen, kidneys, the supraclavicular, hilar and paraaortic glands, and, in two of the patients, also the axillary and inguinal lymph nodes).

No epithelioid cell granulomatosis was present in patients with adenocarcinoma or in those who had not received radiotherapy. The patients have been classified in the table according to age, stage of disease, metastases to the lymph nodes and interval between termination of radiotherapy and operation.

Histologic findings. The appearances resembled those of generalized sarcoidosis. Pale, swollen epithelioid cells in rounded foci, often with giant cells of the Langhan or foreign body type were present. The lymph nodes had signs suggesting more or less severe sinus catarrh with dilated sinuses, containing pale, swollen endothelial cells and a relatively small number of lymphocytes. Conditions transitional between sinus catarrh and well defined epithelioid cell granulomas with or without giant cells were sometimes present.

Discussion

Epithelioid cell granulomatosis was evident in 5.5 % of the patients and agrees well with the figure given by GORTON & LINELL (7.9 %) for a similar series collected during the 1948—1954 period. It seems remarkable however

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DESTRUCTION OF THE HYPOPHYSIS WITH IMPLANTS OF PURE ^{90}Y METAL

by

GUSTAF NOTTER OLOF MELANDER and LARS JOHANSSON

Destruction of the pituitary gland by implantation of isotopes is nowadays the usual technique for the elimination of hypophyseal hormonal activity. However it is difficult to achieve complete cessation of the pituitary function due to the special topography of the hypophysis and its high radioresistance in relation to that of the surrounding tissues.

A radiation dose of 70 000 to 100 000 rad delivered in 10 to 14 days is required to produce necrosis in normal pituitary tissue (RASMUSSON et coll 1953, NOTTER 1959). When applying these doses sufficient protection of the surrounding tissues can be obtained only by using pure β emitters such as ^{90}Y and ^{32}P.

Two types of complications may develop after interstitial irradiation of the hypophysis damage to the cranial nerves and cerebrospinal rhinorrhoea. The first may be avoided by exact implantation of the isotopes but the second is unpredictable and is caused by radiation injury to the diaphragma sellae and the anterior wall of the sella. We therefore have tried to diminish the trauma in the latter by *decreasing* the diameter of the implants from 1.0 to 0.5 mm. The yttrium oxide cylinders of this dimension became too fragile however and we therefore employed the pure yttrium metal which is harder

Submitted for publication 21 February 1967

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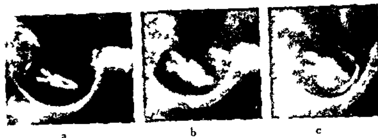
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Lateral roentgenograms of the sella (a) immediately after implantation of four ^{90}Y metal cylinders in the hypophysis and (b) 14 days after the implantation when partial disintegration of the metal cylinders had occurred. After injection into the sella of paraffin wax containing gold powder for treatment of cerebrospinal rhinorrhoea the mixture could be seen as a thin layer on the anterior surface of the hypophysis and in the sella wall (c)

implants. Impurities of about 0.01 % tantalum and less than 0.001 % terbium were also present in the metal.

By activation analysis of the metal cylinders the γ activity peaks were identified as those of ^{160}Tb (half life 73 days), of ^{165}Dy (half life 2.3 hours) and of ^{182}Ta (half life 115 days).

By delaying the implantation until 40 hours after the activation of the implants, the dose contribution from the ^{165}Dy activity was completely avoided. The radiation dose from ^{160}Tb is negligible. The additional radiation dose from ^{182}Ta can be diminished by using a high neutron flux and a short irradiation time. The rods were therefore irradiated for about 1.5 hours in a neutron flux of 1.8×10^{14} neutrons/cm^2/second.

The dose increase from the ^{182}Ta contamination at 1 cm distance from the periphery of the partially disintegrated cylinder may reach about 3 rad during the first 14 days after implantation and about 30 rad after complete decay. This is roughly of the same magnitude as the Bremsstrahlung from the ^{90}Y (NOTTER 1959), and is thus of no practical importance.

Although negligible in relation to the total radiation dose the ^{182}Ta contamination has to be taken into account for a long time as an additional background source when determining radioiodine uptake in the thyroid after implantation.

Discussion

The degree of pituitary destruction is related to the accuracy of isotope positioning in the gland. However after implanting ^{90}Y metal, the dose distribution changes in a non predictable and uncontrolled manner by the varying disintegration and spread of the cylinder within the pituitary gland making

These metal cylinders partly disintegrated in contact with blood and interstitial fluid, however, and this increased the radiation dose to the periphery of the gland and facilitated total destruction but also caused difficulties in dosimetry. Since this behaviour of yttrium metal in human tissue was unexpected we felt justified *in publishing our observation*.

Material and Methods. Yttrium metal has been implanted since March 1964 in 19 patients according to the technique described by NOTTER (1959). Fifteen of the patients had advanced breast cancer, one acromegaly, and three patients had juvenile diabetes mellitus with vascular complications. As a rule 6 mm long and 0.5 mm thick cylinders were inserted bilaterally 3 to 4 mm from the midline. If the sella was longer than 10 mm, two cylinders 4 mm long were implanted on each side (see accompanying figure). The activity of the implants varied between 2 and 3 mCi. After implantation, roentgenograms of the sella were obtained every third day for three weeks. Any possible leakage and contamination of the surrounding tissues were checked. Blood and cerebrospinal fluid of three patients were examined spectrometrically and counted with a 2 1/2" × 3" NaI (Tl) well type scintillation counter.

Results

Complete loss of pituitary hormonal activity was achieved in *14 of the 19* patients by implantation of ^{90}Y metal cylinders into the hypophysis. This included disappearance of the urinary excretion of gonadotrophins, a radio-iodine uptake in the thyroid of under 15 %, low PBI values and development of cortisone deficiency 10 to 12 days after the implantation.

In the first two patients of this series, the defects in the anterior wall of the sella were blocked by titanium screws, using the technique of FORREST et coll. (1958), no screws were inserted in the subsequent patients. Cerebrospinal rhinorrhoea developed in five of the latter but ceased spontaneously in two of them. Two other patients were treated by intrasellar injection of paraffin wax, and this stopped the leakage (see illustration).

Roentgenograms obtained after implantation indicated that the cylinders disintegrated to various degrees, probably depending on their contact with blood and fluid in the tissues. Spectrometric determination and scintillation measurements in samples of blood and cerebrospinal fluid from three patients taken 1 to 20 days after implantation, revealed no evidence of leakage or contamination by ^{90}Y *outside the hypophysis*.

Spectrography and photospectrometry of the yttrium metal used in this series disclosed impurities of 0.04 % dysprosium compared with 0.0017 % in the highly purified Y_2O_3 powder generally used for preparation of the

RÉSUMÉ

Dix neuf malades atteints de cancer du sein avancé d acromégalie ou de diabete sucré juvénile avec complications vasculaires ont eté traités par implantation bilaterale dans l hypophyse de cylindres d yttrium métal ayant chacun une activité de 2 a 3 mCi L activité hormonale de l hypophyse a été complement supprimée chez 14 de ces malades L examen spectrométrique et les mesures de radioactivite n ont pas montré de contamination des tissus environnants du sang ni du liquide céphalo-rachidien par l yttrium 90

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exact dosimetry impossible Radioactivity measurements of cerebrospinal fluid and blood have not shown contamination outside the hypophysis, and careful studies of the patients in this series have not given evidence of radiation damage of the cranial nerves after bilateral implantation of 2 to 3 mCi ^{90}Y cylinders

Contrary to our expectations, the incidence of cerebrospinal leakage was not diminished by causing less trauma of the front wall of the sella by way of decreasing the diameter of the implant to 0 5 mm Leakage developed in five of the 19 patients This complication was treated by intrasellar injection of paraffin according to the suggestion of HAYEM & JURET (1962) We are using a mixture of paraffin wax and either Au or Y_2O_3 powder to make it visible in fluoroscopy This mixture is injected through a specially manufactured, electrically heated, cannula, permitting slow injection of small amounts of the paraffin wax mixture (0 5 ml) into the sella (NOTTER et coll 1967) *This technique was used in two patients with cerebrospinal leakage and in both* patients the leakage ceased (see the accompanying figure) The paraffin wax mixture is now injected prophylactically in all patients after implantation and has proved effective

The screw implantation technique suggested by TALAIRACH et coll (1956) and FORREST et coll (1958) is no longer used in our department It diminished the frequency of rhinorrhoea but failed to afford total protection from it Bone resorption around the screw frequently caused it to drop out of the sella wall and thus led to late cerebrospinal rhinorrhoea

During the last year we have preferred to irradiate the pituitary gland by insertion of a ^{90}Sr needle applicator which seems preferable for several reasons (HOLMER et coll 1967)

SUMMARY

Nineteen patients with advanced mammary carcinoma acromegaly, or juvenile diabetes mellitus with vascular complications were treated by bilateral pituitary implantation of yttrium metal cylinders each of an activity of 2 to 3 mCi Complete loss of pituitary hormonal activity was achieved in 14 of the patients No contamination of the surrounding tissues blood or cerebrospinal fluid with ^{90}Y could be observed by spectrometric studies or radioactivity measurements

ZUSAMMENFASSUNG

Neunzehn Patienten mit fortgeschrittenem Brustkrebs Akromegalie oder juvenilem Diabetes mellitus mit Gefässveränderungen wurden mit bilateraler Implantation von 2 bis 3 mCi Yttrium Metallzylindern behandelt Bei 14 dieser Patienten ging die hypophysäre Hormonausscheidung vollständig verloren Keine Kontamination des umgebenden Gewebes des Blutes oder der Zerebrospinalflussigkeit mit ^{90}Y konnte bei spektrographischen Studien oder Radioaktivitätsmessungen festgestellt werden

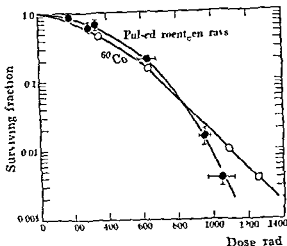


Fig. 1. Survival curves for cultured human kidney cells exposed to ^{60}Co gamma rays at 150 ± 10 rad/min (open circles) and pulsed 10 MV roentgen rays with the total dose being delivered in 3×10^{-8} seconds (solid circles), both under aerated conditions.

Material and Methods. The human kidney cells line T1 originally obtained from BARENDSEN used in these experiments were serially propagated in Eagle's Minimum essential medium and 10 % fetal bovine serum. We irradiated six-to-eight hour single cell cultures growing in 35 mm plastic petri dishes on day old feeder layers of 5×10^4 irradiated (4 000 rad) cells per 35 mm dish.

We used 10 MV roentgen rays generated from a Physics International pulsed electron accelerator in the dose rate range of 10^{11} to 10^{13} rad/min. Each total dose was delivered in a single pulse of 3×10^{-8} seconds duration. For comparison we used ^{60}Co gamma rays at a dose rate of 150 ± 10 rad/min. For both radiations the dose delivered to each group of exposed cultures was determined by LiF thermoluminescence, a method found to be dose rate independent in the range used. Dosimetry capsules and cultures were simultaneously exposed to each dose. Both radiations were filtered by one inch of polyethylene.

The petri dishes containing the cells to be irradiated were mounted in a mylar film faced aluminum exposure wheel (TODD 1966). The medium was removed from the petri dishes just prior to irradiation and the dishes were exposed vertically so that they were perpendicular to the incident radiation beams. In those experiments in which oxygen was removed, high purity nitrogen was passed over the cultures for 20 min prior to exposure. Subsequent to exposure the medium was replaced and the cultures were incubated at 37° C and fed with fresh medium every 5 days until visible colonies developed (~ 2 weeks). Surviving fractions were determined on the basis of colony counts in exposed and control cultures.

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PULSED HIGH-INTENSITY ROENTGEN RAYS

Inactivation of human cells cultured in vitro and limitations on usefulness in radiotherapy

by

PAUL TODD, H. SAUL WINCHELL, JOSÉ M. FEOLA and GARY L. JONES

The suggestion that neoplastic cells are frequently more hypoxic than their normal counterparts, in conjunction with the observation that hypoxic mammalian cells are partially protected from effects of ionizing radiation (DEWEY 1960), has stimulated efforts to seek radiation, the action of which is inpedendent of the presence of oxygen. Some decrease in the oxygen effect with the use of high intensity electron beams has been observed in chemical systems (ROTBLAT & SUTTON 1960), and in bacteria (DEWEY & BOAG 1959), and with high intensity proton beams in water (SHALEK & BONNER 1953). Decreased incidence of chromosome breakage at high radiation dose rates has also been reported (KIRBY SMITH & DOLPHIN 1958).

If the reduced oxygen effects noted in these experiments with high intensity radiations are to be applicable in clinical radiotherapy, such effects must be present within the appropriate dose range for human treatment. In addition, therapeutic applicability requires the use of radiation with adequate penetration. The recent availability of linear accelerators for the production of high energy, high intensity photons suggested experiments to determine the dose dependency of radiation induced inhibition of colony formation by cultured human cells under aerated and anoxic conditions. Our experimental results define the limitations of such high intensity radiation in human radiotherapy.

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eliminating the oxygen effect If the mechanism whereby high intensity reduces the oxygen effect is the use up of available intracellular oxygen at a rate greater than the diffusion of available oxygen into the irradiated volume then the minimum dose rate (10^6 rad/s) obtained by SHALEK & BONNER) is a measure of the rate of oxygen diffusion into the irradiated volume

DEWEY & BOAG, using dose rates in excess of 10^9 rad/s (actually about 10^{10} rad/s) found that doses greater than 13 000 rad were adequate for eliminating the effect of 1 % oxygen in nitrogen in irradiated cultures of the bacterium *Serratia marcescens* If we take the value of 13 000 rad as representing the minimum dose required for the use up of intracellular oxygen at this partial pressure (about 7 6 mm Hg), then one would anticipate a required dose of 260 000 rad (20 × 13 000) to use up the intracellular oxygen at atmospheric pressure (about 152 mm Hg) Recently EPP, WEISS & FENLON (1967) determined that the threshold for oxygen use up in bacterial strain *E coli* B/r in air is about 60 000 rad

It is therefore not surprising that the experiments we describe in this work did not demonstrate a reduced oxygen effect under aerated conditions at dose rates of 10^{11} to 10^1 rad/s and in the dose range of 200 to 1 050 rad

On the basis of the quantitative considerations just presented an estimation may be made of the required partial pressure of oxygen in tissue to allow complete oxygen use up by therapeutically usable radiation doses If we assume 2 000 rad to be the largest single acceptable therapeutic dose then a high intensity radiation pulse (delivered at more than 10^9 rad/s) of this magnitude would require that the oxygen partial pressure in the irradiated tissue be less than 1 1 mm Hg to insure use up of the residual oxygen with resultant elimination of the oxygen effect Therefore, in order to utilize in radiotherapy the diminished oxygen effect seen in high intensity radiation experiments it would be necessary to reduce the partial pressure of oxygen in the target area tissue to about 1 1 mm Hg for the duration of the radiation pulse Such a procedure is limited by considerations of the human physiologic effects of temporary extreme hypoxia

Acknowledgements

We are greatly indebted to Mrs C L Boerke and Mrs W M Jackson for unstinting laboratory assistance and to Mr B Bernstein and the staff of Physics International San Leandro California for performing the irradiations and dosimetry and for their generous sharing of their facilities and equipment This work was supported by NASA and AEC

SUMMARY

Pulsed 10 MV roentgen rays administered at dose rates of 10^{11} to 10^{12} rad/s and in the total dose range of 200 to 1 050 rad/pulse did not differ significantly from ^{60}Co gamma rays in their ability to inactivate aerated cultured human cells It is estimated that a total dose

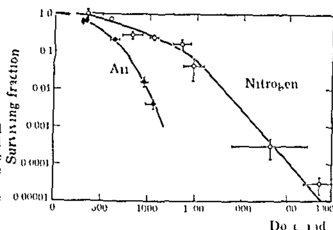


Fig 2 Survival curves for cultured human kidney cells exposed to pulsed 10 MV roentgen rays The air curve is the one shown in fig 1 and the nitrogen curve differs in that purified nitrogen was passed over the cells for 20 minutes prior to irradiation

Results

Survival curves for cells exposed to pulsed roentgen rays and ^{60}Co gamma rays under aerated conditions are presented in Fig 1 Vertical error bars represent the standard errors of mean survival propagated from the relative errors of the mean colony counts on control and irradiated plates Horizontal error bars represent standard deviations of doses determined by the multiple (9 or more) LiF dosimeters used in measuring the dose at each individual dose point The dose rate in rad/s at each dose of pulsed roentgen rays was different and was equivalent to the dose at that point divided by 3×10^{-8} seconds The highest dose rate represented in this graph is approximately 3×10^{11} rad/s The two curves of Fig 1 do not differ significantly considering the experimental conditions

The survival curve for cells exposed to pulsed roentgen rays while in a nitrogen atmosphere is presented in Fig 2 and compared with that obtained under aerated conditions The results suggest that fully anoxic conditions were not achieved in the experiment, since the ratio of doses in nitrogen to those in air required for equivalent survival is less than that anticipated under complete anoxia However, it can be concluded that the effect of oxygen at atmospheric pressure did not disappear at these radiation intensities

Discussion

SHALEK & BONNER, using hydrogen peroxide formation in pure water as their end point at total proton doses in excess of 10^7 rad, found that the difference between yields in air saturated water and helium saturated water disappeared at dose rates greater than 10^9 rad/s These published observations suggest that all ionization produced at intensities greater than 10^9 rad/s is equally effective in

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PATHOLOGIC EFFECTS OF DIFFERENT DOSES OF ^{90}Sr IN MICE

Development of carcinomas in the mucous membranes of the head

by

AGNAR NILSSON

Much work has been done on ^{90}Sr induced neoplasms but it seems that the attention has been mainly concentrated on the induction of osteosarcomas in the skeleton for a study of the histogenesis and development of such lesions and their possible dose dependency (ANDERSON, ZANDER & KUZMA 1956, FINKEL 1959, FINKEL & BISKIS 1959, FINKEL, BERGSTRAND & BISKIS 1961, KOWALEWSKI & RODIN 1964, NILSSON 1962, LITVINOV 1963, OWEN, SISSONS & VAUGHAN 1957 and others). With respect to skeletal malignancies the problem of dose relationships has not yet been unambiguously solved and even less is known concerning neoplasms deriving from other tissues such at hematopoietic organs and mucous membranes in close contact with bone.

A comprehensive study has been made in mice on dose relationships and the pathologic effects and carcinogenic influence of varied doses of ^{90}Sr, in particular on the skeleton, the hematopoietic tissues and the mucous membranes of the head. The results of these investigations will be reported in separate papers, the present

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of 260 000 rad delivered at dose rates greater than 10^8 rad/s is necessary to eliminate the oxygen effect in aerated cells and that at dose rates greater than 10^8 rad/s the partial pressure of oxygen in tissue would have to be reduced to less than about 1.1 mm Hg prior to irradiation to eliminate the oxygen effect.

ZUSAMMENFASSUNG

Pulsierende 10 MV Röntgenstrahlen bei Dosisverhältnissen von 10^{11} bis 10^{1} rad/s und bei Dosen von 200 bis 1 050 rad/Puls waren nicht signifikant verschieden von ^{60}Co Gammastrahlen für die Inaktivierung von Menschenzellen in aerobischer Kultur. Es wurde berechnet, dass man, um den Sauerstoffeffekt bei Dosisverhältnissen grösser als 10^8 rad/s zu beseitigen, mindestens 260 000 rad benötigt. Für die Beseitigung des Sauerstoffeffekts bei Dosisverhältnissen grösser als 10^8 rad/s muss der Sauerstoffdruck weniger als 1.1 mm Hg sein.

RÉSUMÉ

Les rayons de roentgen pulsés de 10 MV administrés avec un débit de dose de 10^{11} à 10^{1} rad/s et à des doses totales allant de 200 à 1 050 rad/impulsion ne présentent pas de différence significative avec les rayons gamma du ^{60}Co en ce qui concerne l'inactivation de cellules humaines en cultures aérées. *Les auteurs estiment qu'il faut une dose totale de* 260 000 rad administrés avec un débit supérieur à 10^9 rad/s pour supprimer l'effet oxygène dans les cellules aérées et que pour des débits de dose supérieurs à 10^9 rad/s il faudrait réduire la pression partielle d'oxygène dans le tissu à moins de 1.1 mm de Hg environ avant l'irradiation pour éliminer l'effet oxygène.

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PATHOLOGIC EFFECTS OF DIFFERENT DOSES OF ^{90}Sr IN MICE

Development of carcinomas in the mucous membranes of the head

by

AGNAR NILSSON

Much work has been done on ^{90}Sr induced neoplasms but it seems that the attention has been mainly concentrated on the induction of osteosarcomas in the skeleton for a study of the histogenesis and development of such lesions and their possible dose dependency (ANDERSON, ZANDER & KUZMA 1956 FINKEL 1959 FINKEL & BISKIS 1959 FINKEL BERGSTRAND & BISKIS 1961 KOWALEWSKI & RODIN 1964 NILSSON 1962 LITVINOV 1963 OWEN, SISSONS & VAUGHAN 1957 and others) With respect to skeletal malignancies the problem of dose relationships has not yet been unambiguously solved, and even less is known concerning neoplasms deriving from other tissues such at hematopoietic organs and mucous membranes in close contact with bone

A comprehensive study has been made in mice on dose relationships and the pathologic effects and carcinogenic influence of varied doses of ^{90}Sr in particular on the skeleton the hematopoietic tissues and the mucous membranes of the head The results of these investigations will be reported in separate papers the present

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of 260 000 rad delivered at dose rates greater than 10^9 rad/s is necessary to eliminate the oxygen effect in aerated cells and that at dose rates greater than 10^9 rad/s the partial pressure of oxygen in tissue would have to be reduced to less than about 1.1 mm Hg prior to irradiation to eliminate the oxygen effect.

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RÉSUMÉ

Les rayons de roentgen pulsés de 10 MV administrés avec un débit de dose de 10^{11} à 10^{12} rad/s et à des doses totales allant de 200 à 1 050 rad/impulsion ne présentent pas de différence significative avec les rayons gamma du ^{60}Co en ce qui concerne l'inactivation de cellules humaines en cultures aérées. Les auteurs estiment qu'il faut une dose totale de 260 000 rad administrés avec un débit supérieur à 10^9 rad/s pour supprimer l'effet oxygène dans les cellules aérées et que pour des débits de dose supérieurs à 10^9 rad/s il faudrait réduire la pression partielle d'oxygène dans le tissu à moins de 1.1 mm de Hg environ avant l'irradiation pour éliminer l'effet oxygène.

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Fig 1 Hard palate Normal mucous membrane from a 225 day-old male mouse van Gieson × 280



Fig 2 Hard palate Mucous membrane with dysplasia and increased mitotic activity *from a mouse killed* 150 days after treatment with 0 8 μCi ^{90}Sr/g bodyweight van Gieson ×280

same room In all the series the mice were housed in groups of ten animals per cage throughout *the whole* experiment

The nomenclature used is in accordance with the general principles in human pathology

Results

Tumour development The earliest morphologically detectable signs of disturbance of the mucous membranes of the ^{90}Sr treated animals consisted of enhanced mitotic activity mostly in the stratum germinativum of the epidermis as com

Table 1

Experimental conditions and doses employed

Dose of ^{90}Sr in μCi/g body weight	Total number of mice	Number of mice killed in groups of 5 every month	Duration of experiment in days	Number of animals dead before sacrifice
1.6	120*	65	300	50
0.8	121	75	360	46
0.4	122	95	480	27
0.2	120**	100	540	17
Control	95	94***	570	1

* Out of these animals five were lost during the experiment
** Out of these animals three were lost during the experiment
*** Only four animals were sacrificed in the last test group

dealing mainly with carcinomas in the mucous membranes of the head. Many of the mice with these carcinomas had osteosarcomas as well, or leukemia, or both. Reports concerning carcinomas are sparse (FINKEL 1959, NILSSON 1962, VAUGHAN 1962) and it has been the aim of this investigation to obtain more precise information on latency time, frequency and sites, histogenesis, development and dose relationships.

Material and Methods. Four groups of CBA mice, 75 days old, were treated intraperitoneally with $^{90}Sr(NO_3)_2$. In addition, a group of 95 animals without ^{90}Sr treatment were used as controls for a study of the natural incidence of tumours. At intervals of 7, 14, 21, and 30 days after injection of ^{90}Sr, and then at monthly intervals, five mice from each group were selected at random and sacrificed, until all mice in each series had been utilized. The experimental conditions and the ^{90}Sr doses employed are recorded in Table 1.

It was not possible to keep the number of killed mice in each dose group the same, because with increasing doses the survival times became much shorter. However, both the sacrificed mice and the mice dead before sacrifice have been investigated, though handled separately.

The mice were decapitated. The head was divided in the median plane during dissection, fixed in Stieve's fluid and decalcified in 20 % formic acid for histologic examination. Conventional methods were used, the sections being stained according to the van Gieson method, with Ehrlich's haematoxylin eosin, and Lillie's azur eosinate. The animals were fed during the experiment on a standard diet ad libitum and kept under similar environmental conditions in the



Fig 1 Hard palate Normal mucous membrane from a 125 day old male mouse van Gieson × 280



Fig 2 Hard palate Mucous membrane with dysplasia and increased mitotic activity from a mouse killed 150 days after treatment with 0 8 μCi ^{90}Sr/g bodyweight van Gieson × 280

same room In all the series the mice were housed in groups of ten animals per cage throughout the whole experiment

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Results

Tumour development The earliest morphologically detectable signs of disturbance of the mucous membranes of the ^{90}Sr treated animals consisted of enhanced mitotic activity mostly in the stratum germinativum of the epidermis as com



Fig. 3. Hard palate. Mucous membrane with increasing degree of hyperplasia and dysplasia with disarranged, slightly atypical basal cells from a mouse 300 days after injection of 0.8 μCi ^{90}Sr/g bodyweight. van Gieson ×280.

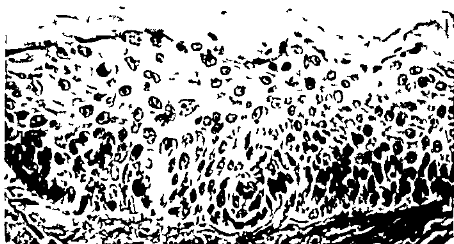


Fig. 4. Hard palate. Mucous membrane with markedly dysplastic changes and predominantly slightly atypical basal cells extending into the stratum spinosum from a mouse 360 days after injection of 0.8 μCi ^{90}Sr/g body weight. van Gieson ×280.

pared to the normal mucous membranes and there was furthermore usually a tendency towards concentration of the mitotic activity to circumscript areas. Slight disarrangement, and often a changed polarity and slightly increased size of the basal cells could be observed. These usually focally situated changes became



Fig 5 Hard palate Mucous membrane with marked dysplasia and scattered moderately atypical nuclei situated in d fferent layers of the epidermis f om a mouse 40 days after injection of 1 6 μCi S /g bodyweight van Gieson ×280



Fig 6 Hard palate Mucou membrane w th carcinoma in situ from a mouse 120 days after inj ct on of 1 6 μC ^{90}Sr/g bodyweight an Gieson ×280

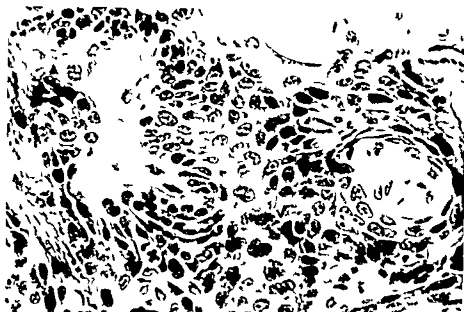


Fig. 7. Oral mucous membrane with a highly differentiated squamous carcinoma from a mouse 270 days after injection of 1.6 μCi ^{90}Sr/g bodyweight. van Gieson. ×280.

successively more accentuated. The basal cell layer was broken up and cell buds or scattered cell elements from this layer began to extend into the stratum spinosum. The basal cells were usually hyperplastic with hyperchromatic and slightly atypical nuclei. Changes of the now mentioned types have in this investigation been termed *dysplasia with slight atypism* (Figs. 2 to 4).

In local foci there was a continuously increasing number of more atypical basal cells extending into all the layers of the epidermis. Giant nuclei also began to appear. In some cases, premature keratinization was evidenced by cells containing eosinophilic homogenous droplets of intracellular keratin. The destruction of the normal histologic structures was extensive. This stage has in the present communication been termed *dysplasia with moderate atypism* (Fig. 5).

In the next stage the cells were of definitely carcinomatous type, and all layers of the epidermis were infiltrated by these. A distinction has, however, been made between *carcinoma in situ* (Fig. 6) and *invasive cancer* (Fig. 7). The first type is represented by local carcinomatous noduli of limited extent, not infiltrating surrounding tissue or the basal membrane.

The epithelium of the tongue of the same animal has been used as an unirradiated histologic control. Since the average ranges of the β particles from ^{90}Sr and its ^{90}Y daughter in soft tissues are, respectively, 0.3 and 2.1 mm, this mucosa



Fig 8 Reg o olf ctoria Nor nal mucous membrane f om a 28ɔ day old mouse van G eson ×4 0



Fig 9 Regio olfactoria M cous membrane from a mouse 270 days after inj ction of 1 6 μCi Sr/g bodywe ght Deplet on of nervous olfactory cells marked sustentacular cells mitotic figure alorg the b sal membrane van G eson ×450

may be regarded as unirradiated in comparison with parts of the oral mucosa irradiated from underlying bone structures

Tumours formed in the cutaneous membranes of the nose follow the same pattern of development as the oral carcinomas In some cases tumour formation has however also been observed in the olfactory membranes The most important early observation was a reduction and a later disappearance of the nervous olfactory cells swelling of the sustentacular cells and the appearance of mitotic



Fig 10 Regio olfactoria Mucous membrane from a mouse 300 days after injection of 1 6 μCi ^{90}Sr/g bodyweight Most of the olfactory nerve cells have disappeared abundance of atypical cells and mitotic figures van Gieson ×450

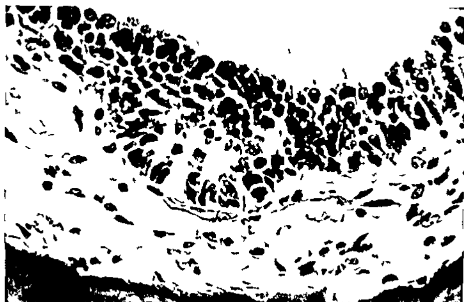


Fig 11 Regio olfactoria Mucous membrane from a mouse 240 days after injection of 1 6 μCi Sr/g bodyweight Bud of atypical cells showing a focal expansion of the basal membrane into underlying connective tissue van Gieson ×450

figures along the basal membrane The cells replacing the nervous elements were usually elongated, hypertrophic and with strongly hyperchromatic nuclei which seemed to invade the mucosa from the basal membrane It seemed to be basal cells that comprised the greater bulk of these cells (Figs 8 to 12)

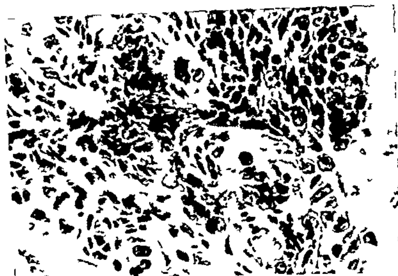


Fig 17 Nasal cavity Invasive carcinoma in a mouse 300 days after injection of 1 6 μCi Sr/g bodyweight van Gieson × 430

The changes successively leading to the development of carcinoma follow nearly the same pattern in the different dose groups They commence earlier however and develop more rapidly with increasing ^{90}Sr doses This is exemplified in Fig 13 representing the results obtained from each group of animals sacrificed at 30 day intervals Only in the highest dose group have carcinomas of the olfactory mucous membrane been detected

Tumour frequency The number of tumours occurring in the different dose groups are recorded in Table 2 and in Fig 14 the accumulated total number of tumours are represented in relation to the time elapsed after the ^{90}Sr administration

A total of 80 carcinomas and carcinomas in situ were found in the whole experiment when the sacrificed mice and the animals dead before sacrifice were counted together Of these 56 or 70 % were found in the 1 6 μCi group, 21 or 26 % in the 0 8 μCi group and only 3 or 4 % in the 0 4 μCi series It should be pointed out that the number of tumours obtained is a minimum since no serial sectionings were performed

Latency time A comparison of the various time intervals between injection of ^{90}Sr and the occurrence of dysplastic changes carcinomas in situ and carcinomas has been made for the different dose groups in Table 3

Table 2

Tumour frequency in the different dose groups

Dose µCi ^{90}Sr/g body weight	Number of mice investigated	Number of sacrificed mice	Number of tumour bearing mice	Total number of tumours	Number of tumours per mouse	Percent mice with tumours
1.6	115	65	38	56	0.49	33.0
0.8	121	75	17	21	0.17	14.0
0.4	122	95	3	3	0.02	2.5
0.2	117	100	0	0	0.00	0.0
Control	95	94	0	0	0.00	0.0

Table 3

Comparison of latency time in the development of dysplastic changes and carcinomas in mucous membranes in the different ^{90}Sr dose groups

Dose µCi ^{90}Sr/g body weight	Dysplasia		Carcinoma in situ + carcinoma			
	Sacrificed animals		Sacrificed animals		Mice dead before sacrifice	
	Number	Days Mean ± SE	Number	Days Mean ± SE	Number	Days Mean ± SE
1.6	17	152 ± 19.0	18	242 ± 11.2	20	232 ± 3.9
0.8	17	249 ± 15.6	11	330 ± 8.1	6	319 ± 8.4
0.4	23	335 ± 16.6	2	465	1	407
0.2	7	497 ± 24.4	0	—	0	—

Table 4

Percentual tumour distribution at different sites

Group	Hard palate	Incisivous part		Nose
		Upper jaw	Lower jaw	
Whole experiment	58.8	11.3	13.8	16.3
1.6 µCi group	60.7	10.7	12.5	16.1
0.8 µCi group	61.9	9.5	9.5	19.0
0.4 µCi group	[illegible]	1.3	2.6	

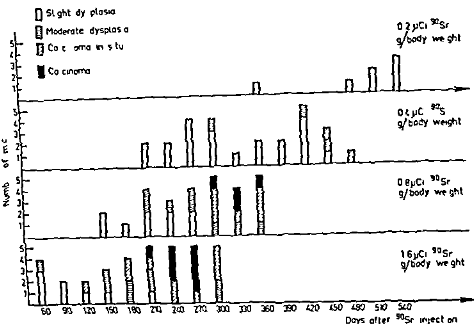


Fig 13 Histograms showing start and development of changes leading to *carcinomas* The mice were killed in groups of five at 30-day intervals

Tumour sites The sites of the carcinomas and carcinomas in situ are shown in Table 4 Out of the total of 80 tumours 47 or 58 8 % were located in the mucous membranes lining the palatine bone The most frequent site was in a limited area adjacent to the termination of the hard palate No tumours were situated in the soft palate and only few in the *rugae* area of the hard palate In an area lining the incisivous part of the mandible 11 tumours or 13 8 % were detected and in the opposite region of the upper jaw 9 or 11 3 % were found Of 13 tumours or 16 3 % in the nasal cavities three were situated in the olfactory region and the remainder in the cutaneous part of the nose

Tumour type All the carcinomas investigated, excepting those in the olfactory region have been of the squamous type The degree of differentiation varied, however Of 31 tumours in the 1 6 μCi group twenty two were highly differentiated squamous carcinomas five were moderate and four were low differentiated Of the 9 tumours in the 0 8 μCi group the corresponding figures were four four and one The carcinomas defined as highly differentiated were strongly keratin producing the moderate type slightly, and the low differentiated tumours did not show any evidence of keratin formation

Discussion

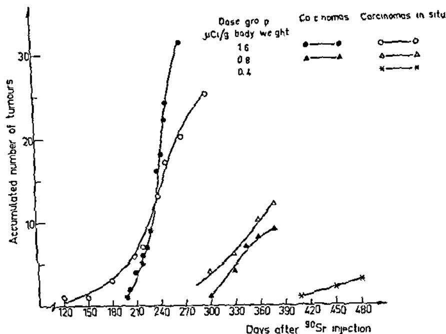
The results of this investigation seem to bear in evidence that the squamous cell carcinomas in the cutaneous membranes of the mouth and nose start at local sites in the stratum germinativum It is possibly basal cell elements, damaged by the irradiation from the underlying bone, which initiate the changes ultimately leading to overt neoplasia

With respect to the mucous membrane from the olfactory region of the nose it also seems possible to assume from the few cases investigated that the lesion started from basally situated cells of epidermal origin In the evaluation of the relationship between these changes and irradiation, the localization of the tumours is of the greatest importance As may be seen from Table 4, most of these tumours emanated from the mucous membrane of the hard palate They were usually formed in small foci in an area between the rugous part and the termination of the hard palate They could also be found around the incisivous part of the upper and lower jaw Histologically, this may be explained by the fact that in these parts the contact between the mucous membranes and the underlying bone structures is very intimate

In contrast to these observations, no carcinomas were detected in the epithelium of the tongue It is also obvious from Table 4 that the dose inside a range between 1 6 and 0 8 μCi of ^{90}Sr/g bodyweight has little influence on tumour localization Exceptions are carcinomas in the olfactory membranes, which have been detected only in the 1 6 μCi group

A comparison of the latency time for development of dysplastic changes as well as carcinomas in situ and carcinomas also seems to indicate dose dependency Thus, dysplastic changes started on an average 90 days earlier in the 1 6 than in the 0 8 μCi group This time relationship still exists if the latter series is compared with the 0 4 μCi group Between the 0 2 and 0 4 μCi groups this time interval was however increased to 162 days (see Table 3) A possible explanation is that the development of dysplastic changes may be delayed for a considerable time by an intact recovery mechanism Also for the carcinomas, the latency time was still approximately 90 days shorter for the 1 6 μCi group as compared to the 0 8 μCi group Between the latter and the 0 4 μCi group, the time interval increased to 135 days It may be pointed out that only carcinomas in situ developed in the 0 4 μCi group If the mice in this group had been allowed to survive for a longer period it seems probable that more tumours would have had time to develop On the other hand, animals given the 0 4 μCi dose seemed to have a greater ability to resist cellular transformations ultimately leading to tumour

Not only the site of the earliest changes and the latency time for tumour



F g 14 Accu nulation of total number of tumours obta ned in the different dose groups

development but also the carcinoma frequency and the total number of tumours obtained seem to indicate a dose relationship (Table 2 Fig 14) Thus there is approximately twice as high values for tumour bearing mice, total number of tumours and percent mice with tumours in the 1 6 μCi as compared to the 0 8 μCi group On the other hand this correlation does not exist between the 0 8 and 0 4 μCi groups but this could possibly be explained by the fact that the mice had not survived long enough to give time for maximum tumour development in the lowest dose group

SUMMARY

Radiostrontium induced carcinomas of the mucous membranes of the head have been studied in mice Four groups were injected with respectively 1 6 0 8 0 4 and 0 2 μCi ^{90}Sr per gram bodyweight The development of carcinoma usually started in the stratum germinativum of the epidermis usually at local sites the most common being the mucous

Discussion

The results of this investigation seem to bear in evidence that the squamous cell carcinomas in the cutaneous membranes of the mouth and nose start at local sites in the stratum germinativum. It is possibly basal cell elements, damaged by the irradiation from the underlying bone, which initiate the changes ultimately leading to overt neoplasia.

With respect to the mucous membrane from the olfactory region of the nose it also seems possible to assume from the few cases investigated that the lesion started from basally situated cells of epidermal origin. In the evaluation of the relationship between these changes and irradiation, the localization of the tumours is of the greatest importance. As may be seen from Table 4, most of these tumours emanated from the mucous membrane of the hard palate. They were usually formed in small foci in an area between the rugous part and the termination of the hard palate. They could also be found around the incisivous part of the upper and lower jaw. Histologically, this may be explained by the fact that in these parts the contact between the mucous membranes and the underlying bone structures is very intimate.

In contrast to these observations no carcinomas were detected in the epithelium of the tongue. It is also obvious from Table 4 that the dose inside a range between 1.6 and 0.8 μCi of ^{90}Sr/g bodyweight has little influence on tumour localization. Exceptions are carcinomas in the olfactory membranes, which have been detected only in the 1.6 μCi group.

A comparison of the latency time for development of dysplastic changes as well as carcinomas in situ and carcinomas also seems to indicate dose dependency. Thus, dysplastic changes started on an average 90 days earlier in the 1.6 than in the 0.8 μCi group. This time relationship still exists if the latter series is compared with the 0.4 μCi group. Between the 0.2 and 0.4 μCi groups this time interval was however increased to 162 days (see Table 3). A possible explanation is that the development of dysplastic changes may be delayed for a considerable time by an intact recovery mechanism. Also for the carcinomas the latency time was still approximately 90 days shorter for the 1.6 μCi group as compared to the 0.8 μCi group. Between the latter and the 0.4 μCi group, the time interval increased to 135 days. It may be pointed out that only carcinomas in situ developed in the 0.4 μCi group. If the mice in this group had been allowed to survive for a longer period it seems probable that more tumours would have had time to develop. On the other hand animals given the 0.4 μCi dose seemed to have a greater ability to resist cellular transformations ultimately leading to tumour.

Not only the site of the earliest changes and the latency time for tumour

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VAUGHAN J Cited from DOUGHERTY

membrane covering the palatine bone A dose dependency seems to exist since with in creasing doses of ^{90}Sr the latency time was shortened and the *tumour frequency aug mented*

ZUSAMMENFASSUNG

Radiostrontium induzierte Karzinome der Schleimhaut des *Kopfes wurden in Mausen* studiert Vier Gruppen wurden je mit 1 6, 0 8 0 4 und 0 2 μ Ci ^{90}Sr per Gramm Korper gewicht intraperitoneal injiziert Die Karzinome Entwicklung fand erst in dem Stratum germinativum der Epidermis statt, meistens innerhalb begrenzter Regionen haufigst in der Schleimhaut die das Gaumenbein bedeckt Eine Dosisabhangigkeit scheint zu bestehen da mit erhohten Dosen von ^{90}Sr die Latenzzeit verkurzt wurde und die Tumor Frequenz gesteigert wurde

RESUME

L auteur a etudie les cancers des muqueuses de la tete induits par le strontium radioactif Quatre groupes de souris ont reçu une injection intraperitoneale de 1 6 0 8 0 4 et 0 2 μCi de ^{90}Sr par gramme de *poids corporel respectivement Les cancers ont commence à se de* velopper dans la couche germinative de l épiderme habituellement en certains sièges dont le plus frequent a ete la muqueuse qui recouvre l os palatin Ces cancers semblent dependre de la dose puisque le temps de latence est raccourci et la frequence des tumeurs augmente avec des doses croissantes de ^{90}Sr

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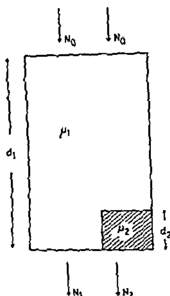


Fig. 1. Diagram illustrating a radiographed object with thickness d_1 containing a volume thickness d_2 with a different mass and/or chemical composition.

gram. A discussion of this complicated matter involving physiology as well as psychology, is beyond the scope of the present paper. However, it is postulated that an optimum signal to noise ratio will be obtained when the differences in photographic density caused by differences in mass or chemistry in the object are as large as possible in the roentgen image. The fulfilment of this condition requires knowledge of how the relationship between mass and/or chemistry differences in the object, and the corresponding differences in photographic density of the roentgen image vary with variations in the physical parameters involved. This problem will now be treated theoretically.

Theoretical considerations

Assume an object (Fig. 1) with thickness d_1 irradiated by N_0 photons per unit area, μ_1 is the linear attenuation coefficient and N_1 the number of photons transmitted through the object per unit area. If the object contains a volume with thickness (d_2) having the linear attenuation coefficient μ_2, the number of transmitted photons per unit area is N_2. Then with narrow beam geometry and monoenergetic radiation the following equations will hold for the attenuation of the radiation:

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DETERMINATION OF SMALL MASS DIFFERENCES IN ROENTGENOGRAPHY

I. Theoretical considerations

by

GUNNAR LYSELL, BENGT K. A. MÅRTENSSON and KARL ÅKE OMNELL

Many pathologic conditions are accompanied by a local change in the mass and/or chemical composition of the body tissues involved. Roentgen examination is a most important tool for the detection and the interpretation of such conditions.

The differential blackening of the roentgen film is a function not only of mass differences within the object and/or differences in its chemical composition but also of several other factors such as the characteristics of the photographic emulsion (and intensifying screens), exposure data and the dark room procedure. *From a diagnostic standpoint it is of importance to gain as much* information as possible from the roentgenograms, i. e. to be able to demonstrate as small pathologic mass differences or differences in chemistry as possible. When a *roentgenogram is evaluated visually, the signal from the image* depicting the pathologic change is dependent not only on the texture of this image but also on distractions or 'noise' from adjacent areas in the roentgeno

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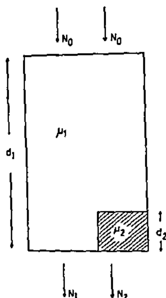


Fig 1 Diagram illustrating a radiographed object with thickness d contain ng a olume thick ness d with a different mass and/or chemical com pos tion

gram A discussion of this complicated matter, involving physiology as well as psychology is beyond the scope of the present paper However it is postulated that an optimum signal to noise ratio will be obtained when the differences in photographic density caused by differences in mass or chemistry in the object are as large as possible in the roentgen image The fulfilment of this condition requires knowledge of how the relationship between mass and/or chemistry differences in the object and the corresponding differences in photographic density of the roentgen image vary with variations in the physical parameters involved This problem will now be treated theoretically

Theoretical considerations

Assume an object (Fig 1) with thickness d_1 irradiated by N_0 photons per unit area μ_1 is the linear attenuation coefficient and N_1 the number of photons transmitted through the object per unit area If the object contains a volume with thickness (d) having the linear attenuation coefficient μ_2 the number of transmitted photons per unit area is N_2 Then with narrow beam geometry and monoenergetic radiation the following equations will hold for the attenuation of the radiation

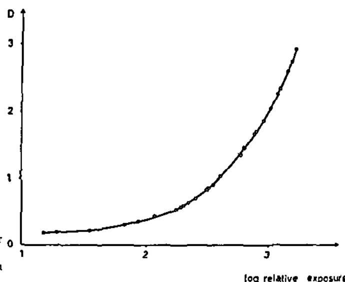


Fig 2 The characteristic curve for Kodak periapical radiatized dental X ray film exposed to roentgen radiation

The ratio between the number of transmitted photons will be

$$\frac{N_2}{N_1}=e^{(\mu_1-\mu_2)d} \tag{1}$$

In roentgendiagnostic work, photographic film is mostly used as a detector for the radiation The characteristic curve (Fig 2) of the roentgen film gives the photographic density (D) as a function of the logarithm of the exposure (X)

At any point, D_1, of the curve we define a function

$$\gamma_{D_1}(D)=\frac{D-D_1}{\log X-\log X_1} \tag{2}$$

where D is a variable point of the curve

From eq (2) we obtain

$$\frac{X}{X_1}=10^{\frac{D-D_1}{\gamma_{D_1}(D)}} \tag{3}$$

For monoenergetic radiation and narrow beam geometry the exposure is directly proportional to the number of photons per unit area Then, from eqs (1) and (3) we obtain

$$10^{\frac{D_2-D_1}{\gamma_{D_1}(D_2)}}=e^{(\mu_1-\mu_2)d}$$

and hence

$$d_2=\frac{(D_2-D_1)\ ln\ 10}{\gamma_{D_1}(D_2)\ (\mu_1-\mu_2)} \tag{4}$$

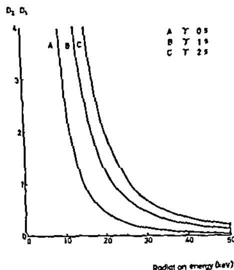


Fig 3 Differences in photographic density as functions of the photon energies in keV at three values of γ Calculation according to eq (4) (d = 0 1 cm)

Thus a photometric evaluation of D_2 and D_1 makes it possible to quantitatively determine d according to eq (4) provided the characteristic film curve the radiation energy and the linear attenuation coefficient are known Eq (4) shows that a volume with thickness d_2 contained in an object with thickness d_1 will influence the difference in photographic density $(D_2—D_1)$, giving higher differences in photographic density with increasing values of γ_D (D_1) and $(\mu_2—\mu_1)$

At densities below a certain D value, which has to be determined experimentally log D as a function of log X will approximately be a straight line The corresponding analytical approximation (NILSSON 1963) is

$$X=B\ g\ Q\ D^{1/a} \tag{5}$$

where X is the exposure B is a constant corresponding to a given radiation quality g is a function (probably a constant) depending on the dark room procedure Q is a constant for a given film type D is the photographic density when the fog and base density has been subtracted and a is a constant For given experimental conditions, eq (5) can be written

$$D=k\ X \tag{6}$$

where k is a constant If in eq (2) the difference log X—log Y_1 tends to zero γ_{D_1} (D) will express the rate of change of D as a function of log Y

(7)

After differentiation of eq. (6) we obtain

$$\frac{d(\ln D)}{d(\ln X)}=a \text{ but}$$

$$\frac{d(\ln D)}{dD}=\frac{1}{D}$$

After substitution, eq. (7) can be written

$$\gamma_{D_1}(D)=\frac{dD}{d(\ln D)}\cdot\frac{d(\ln D)}{d(\ln X)}\cdot\frac{1}{\log e}=D\cdot a\cdot\frac{1}{\log e} \quad (8)$$

Provided the difference (D_2-D_1) is sufficiently small, substitution for $\gamma_{D_1}(D)$ in eq. (4) gives

$$d_2=\frac{D_2-D_1}{a\,D\,(\mu_1-\mu_2)} \quad (9)$$

Discussion

For the sake of simplicity, in the theoretical considerations presented, a thickness difference in the object has been represented by a difference in mass and/or a difference in chemical composition. Accordingly, linear attenuation coefficients have been used instead of mass attenuation coefficients.

The relation between a thickness difference in a radiographed object, and the corresponding difference in photographic density of the roentgen film, is deduced from eqs. (4) and (9).

While eq. (4) is valid for all types of roentgen film and for the entire characteristic film curve before the solarisation, eq. (9) holds at least for direct exposure films and for the range of photographic densities in which eq. (5) may be applied. Another condition for application of eq. (9) is that the thickness and photographic density differences have to be small enough to allow differential calculations. Consequently, since it is difficult to employ γ determinations with precision at small density differences, eq. (9) offers the advantage that *γ determinations do not have to be involved*. On the contrary, an experimental determination of a must be performed. However, since a, following eq. (6), is the inclination of the straight line representing the characteristic curve in a log log diagram, it is easy to evaluate.

According to eq. (4), if the thickness difference is given, the corresponding difference in photographic density will increase with increasing γ value and with decreasing energy. This holds if absorption edges will not cause $(\mu_1-\mu_2)$ to decrease with decreasing energy. In Fig. 3, the result of a calculation at

three different γ values of thickness differences of aluminium in air is presented At 30 keV the difference in photographic density, corresponding to a thickness difference of 0 1 cm at $\gamma = 0\ 5$ will be one third of that at $\gamma = 1\ 5$ These two $\gamma_D(D)$ values will be found at $D = 0\ 2$ and $D = 0\ 8$, respectively, for the characteristic curve in Fig 2 giving an exposure ratio of about 1 4 5 Thus in the example given a three fold increase in difference in photographic density will be obtained at the cost of a more than four fold exposure That is to say a three fold increase in detectability will be obtained with a more than four fold exposure

Eqs (4) and (9) are valid for monoenergetic photons and narrow beam geometry However, in roentgen diagnostics one has to utilize polyenergetic roentgen radiation Provided the effect of the thickness difference on the spectral distribution of the roentgen radiation can be neglected eqs (4) and (9) are valid also for polyenergetic radiation Then the difference between the linear attenuation coefficients $(\mu_1 - \mu_2)$ according to eqs (4) and (9) has to be substituted by the corresponding difference $\overline{\mu_1 - \mu_2}$

$$\text{where } \overline{\mu_1 - \mu_2} = \frac{1}{N} \int_0^\infty (\mu_1 - \mu_2)\, N(h\nu)\, d(h\nu)$$

where N is the total number of photons of the spectrum and $N(h\nu)$ is the number of photons with energies between $h\nu$ and $h\nu + d(h\nu)$

In roentgendiagnostic work it is impossible to prevent all scattered radiation from reaching the film emulsion Consequently eqs (4) and (9) have to be corrected for the photographic density created by the *scattered radiation* Such corrections are in a complicated manner dependent both on the spectral *distribution* of the radiation and the radiation geometry Accordingly the *influence of* scattered radiation on eqs (4) and (9) has to be studied experimentally

Eqs (4) and (9) give the important quantitative relationship between a thickness difference in a radiographed object and the corresponding difference in *photographic density* of the roentgen image In order to optimize the roentgendiagnostic procedure when small mass differences are examined the influence of such factors as radiation geometry exposure time and radiation dose has to be studied experimentally utilizing eqs (4) and (9) as a basis

SUMMARY

The relation between a thickness difference in a radiographed object and the corresponding difference in photographic density *in the* roentgenogram varies with the physical parameters involved A theoretical treatment of this problem is presented

ZUSAMMENFASSUNG

Die Beziehung zwischen dem Unterschied in der Dicke eines bestrahlten Objekts und dem entsprechenden Unterschied in der photographischen Schwarzung variiert mit Variationen in den physikalischen Parametern. Eine theoretische Behandlung dieses Problems wird vorgelegt.

RÉSUMÉ

La relation entre une différence d'épaisseur dans un objet radiographié et la différence de densité photographique correspondante varie quand varient les paramètres physiques concernés. Ce travail a pour objet une étude théorique de ce problème.

REFERENCE

NILSSON, R. γ dose measurements with the Dupont 508 film in mixed radiation fields. AB Atomenergi Studsvik Internal report RFA 487, 1963.

FROM THE INSTITUTE OF RADIOPHYSICS (DIRECTOR PROF R WALSTAM) KAROLINSKA SJUKHUSET STOCKHOLM, SWEDEN

COMMERCIAL PHOTODIODES AS GAMMA AND ROENTGEN RAY DOSIMETERS

by

P E ÅSARD and G BAARSEN

There has always been a need in radiotherapy to check the doses given to patients The development in radiotherapy and radiophysics has led to more accurate estimates of doses partly because of the use of external beam treatment with high energy photons which facilitates dose calculations compared to conventional roentgen ray treatments and partly because of the fact that dose planning is now being more widely used Individual dose planning does not however in all cases permit a sufficiently accurate determination of the dose at different points during the treatment of a patient It is therefore highly desirable to be able to measure the dose directly The necessity for measurement is particularly obvious when the thorax region has to be irradiated and when it is required to know the dose to the rectum and bladder for application of radium or similar sources in the vagina and uterus

An important requirement for a radiation detector intended for use in in vivo measurements is that its dimensions be as small as possible Sieverts Bg-chambers (0 5 cm in diameter and 2 cm long) are used at Radiumhemmet for measurements in the esophagus and rectum and a Siemens Gammameter with a CdS crystal is used for measurement of dose rates in gynecologic treat

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ments with radium. In the last years, however, new dosimeters have been introduced which seem suitable for these purposes. These are of the solid state type, the thermoluminescense detector, and the p-n junction detector. The p-n junction detector has the advantage over the LiF dosimeter that the dose rate during treatment can be read directly on an instrument. The measuring equipment for the p-n junction detector can in most cases be an ordinary DC voltmeter and no bias voltage is needed. This eliminates the risk of electrical shock to the patient if the isolation should become damaged. The advantages over the ionization chamber is the higher sensitivity per volume, the robustness, and the fast response.

Details of investigations on commercial photodiodes and silicon solar cells have been published (MOODY et coll. 1958, CALKINGS 1962, GULDBRANSEN & MADSEN 1962, WHELPTON & WATSON 1963 and JONES 1963). These results have stimulated us to investigate some other diodes in order to estimate their usefulness in clinical dosimetry. The silicon diodes tested were Siemens BPY 11 and BPY 100, and two Hoffmann solar cells, type B 120 CG 9 and N 120 CG 9, the latter described as radiation resistant by the manufacturers. The parameters investigated were (1) sensitivity, (2) exposure rate dependence, (3) temperature dependence, (4) energy dependence, and (5) radiation damage.

Function of the diode. The solid state diode consists of a p- and n-layer separated by a depletion layer. This depletion layer is produced when the holes diffuse to the n-layer and the electrons to the p-layer, causing a voltage drop between the two layers. If a bias voltage is applied with positive polarity to the n-layer and negative to the p-layer, the depletion layer is increased. The sensitive part of the diode for ionizing radiation is the depletion layer and a small region around it determined by the diffusing length for the minority carriers. Charged particles produced by Compton, photo- and Auger processes interact with the diode by exciting electrons up to the conducting band from the valence band, and corresponding holes are produced in the valence band. The charges produced in the sensitive region of the diode drift under the influence of the electric field in the depletion region producing a current through the diode.

No bias voltage is needed because the radiation produced holes are driven to the p-layer and the electrons to the n-layer, generating a photo voltage biasing the diode in the forward direction. If the diode is connected to an instrument with a load resistance R_L, part of the current goes through the instrument in reverse direction, and the other part leaks through the diode in a forward direction. If $R_L \rightarrow 0$, the whole current goes through the instrument, and if $R_L \rightarrow \infty$, the instrument measures the open circuit voltage.

SCHARF & SPARROW (1964) have calculated the photovoltaic current,

produced by roentgen rays in a p n junction, by methods similar to those applied for calculation of the photoresponse of a junction to visible light In current notation, the function of a diode can be described as follows

If I is the photovoltaic output current I_g the current generated by the radiation and I_f the junction leakage current flowing in the forward direction then

$$I = I_g - I_f \quad (1)$$

and I_g is proportional to the exposure rate An approximate equation for I_f is

$$I_f = I_o \left[e^{qV/kT} - 1\right] \quad (2)$$

I_o being the diode saturation current in reverse direction q the electronic charge V the forward voltage between cell terminals under closed circuit conditions k the BOLTZMANN constant and T the absolute temperature

If equations (1) and (2) are combined one obtains

$$V = \frac{kT}{q} \ln\left[\frac{I_g - I}{I_o} + 1\right]$$

When the load resistance $R_L \to \infty$ (i e $I \to 0$) V will be the open circuit voltage which is not proportional to the exposure rate and is temperature dependent The open circuit voltage is however approximately linear to the exposure rate when $\frac{eV}{kT} << 1$ (i e $V << 25$ mV at room temperature) Linearity of the photovoltage with exposure rate is also obtained when the leakage current $I_f = 0$ i e when $R_L \to 0$ (i e $V \to 0$) In that case

$$V = IR_L = I_g \; R_L$$

is measured under short circuit conditions

Measuring techniques Maximum sensitivity is achieved if pulse counting is used but this requires a more complicated instrumental set up than simple DC-measurements of the current or voltage and it cannot be used at high dose rates The simplest method is to measure the open circuit voltage and this is also a more sensitive method than measuring the short circuit current Disadvantages are the temperature dependence and the non linearity with dose rate At small intensities however the open circuit voltage is approximately proportional to the exposure rate as pointed out above

Current measurements can also be made with reverse bias applied to the diode but JONES (1963) found that the ratio of the signal to the leakage current decreased with increased bias -

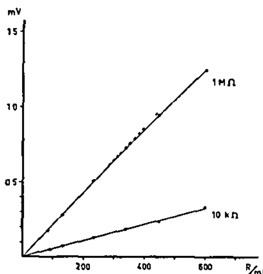


Fig 1 Exposure rate dependence of a BPY 11 diode irradiated with a ⁶⁰Co beam at different load resistances The signal for the 1 MΩ curve must be multiplied by 10

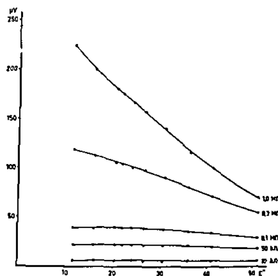


Fig 2 Temperature dependence of a BPY 11 diode at different load resistances

The dimensions of our BPY 11 and BPY 100 diodes are 4 8 mm × 2 2 mm × 0 9 mm, when used for measurements in water phantoms and for energy dependence measurements they were coated with epoxy resin and painted black The Hoffmann diodes are 10 mm × 4 mm × 0 5 mm A Hewlett Packard DC microvoltammeter (425A) has been used in all the measurements

Exposure rate dependence The voltage from a BPY 11 diode irradiated with ⁶⁰Co gamma radiation was measured at different exposure rates and load-resistances between 10 kΩ and 1 MΩ As may be seen from Fig 1, non linearity is present at exposure rates higher than about 200 R/min at 1 MΩ in load resistance This means that if the diode is used for a roentgen beam with a HVL of say 0 1 mm Cu, the deviation from a linear relationship between exposure rate and voltage is seen already at about 35 R/min as a result of the energy dependence of the diode At 10 kΩ in load resistance the curve is linear, at least to the highest exposure rate measured (~600 R/min)

Temperature dependence In order to measure the temperature dependence, the diodes (BPY 11) were immersed in a water bath in which the temperature could be controlled to ±0 5° C The diodes were irradiated with ⁶⁰Co gamma radiation with an exposure rate of about 10 R/min The temperature range was 10° to 50° C, and the load resistance was varied between 1 MΩ and 10 kΩ

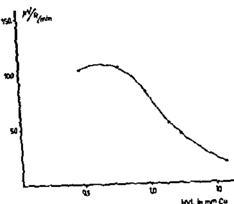


Fig 3 Energy dependence of a BPY 11 diode for Co irradiation The different HVL values correspond to 100 kV 1 mm Al 140 kV 4 mm Al 175 kV 0 5 mm Cu+1 mm Al 200 kV 0 4 mm Sn+1 mm Al 2 0 kV 1 mm Al+0 6 mm Sn

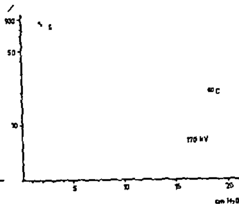


Fig 4 Depth doses measured with an ionization chamber (×) and a BPY 11 diode (O) for a Co beam (SSD 60 cm) and a 170 kV roentgen beam with Thoreaus filter (FSD 40 cm) The curves are normalized to 5 cm depth A = 10 cm × 10 cm

As will be seen from Fig 2 the sensitivity of the diode decreases with the temperature at high load resistances but becomes independent of temperature when the load resistance is 10 kΩ i e when the short circuit current is measured Of the four diodes investigated one showed a similar response to the diode as in Fig 2 but the other two showed a slow increase up to about 26 C and then a decrease in response The latter two diodes were independent of temperature at 100 kΩ due to differences in junction resistance as compared to the first diode

Energy dependence The measurements were made free in air with a BPY 11 diode and the exposure was measured with a Victoreen chamber of known energy dependence The load resistance for the diode was 1 MΩ The dose rate in all the measurements was kept so low that the signal from the diode was always less than 1 mV, this in order to eliminate any faults depending on non linearity The temperature was controlled to ±1° C In Fig 3 the sensitivity of the diode is plotted as a function of HVL The diode is about 6 times (5 7) more sensitive when irradiated with a beam with HVL 0 1 mm Cu than when irradiated with ^{60}Co WHELPTON & WATSON (1963) changed the energy response of their probe by making suitable filters which caused the curve representing the energy range between roentgen radiation with HVL 1 mm Cu and ^{60}Co gamma radiation to appear practically flat

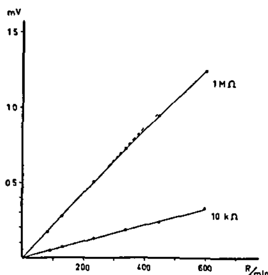


Fig. 1. Exposure rate dependence of a BPY 11 diode irradiated with a ^{60}Co beam at different load resistances. The signal for the 1 MΩ curve must be multiplied by 10.

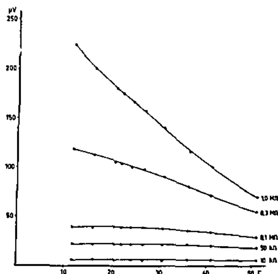


Fig. 2. Temperature dependence of a BPY 11 diode at different load resistances.

The dimensions of our BPY 11 and BPY 100 diodes are 4.8 mm × 2.2 mm × 0.9 mm; when used for measurements in water phantoms and for energy dependence measurements they were coated with epoxy resin and painted black. The Hoffmann diodes are 10 mm × 4 mm × 0.5 mm. A Hewlett Packard DC microvoltammeter (425A) has been used in all the measurements.

Exposure rate dependence. The voltage from a BPY 11 diode irradiated with ^{60}Co gamma radiation was measured at different exposure rates and load-resistances between 10 kΩ and 1 MΩ. As may be seen from Fig. 1, non linearity is present at exposure rates higher than about 200 R/min at 1 MΩ in load resistance. This means that if the diode is used for a roentgen beam with a HVL of say 0.1 mm Cu, the deviation from a linear relationship between exposure rate and voltage is seen already at about 35 R/min as a result of the energy dependence of the diode. At 10 kΩ in load resistance the curve is linear, at least to the highest exposure rate measured (~600 R/min).

Temperature dependence. In order to measure the temperature dependence, the diodes (BPY 11) were immersed in a water bath in which the temperature could be controlled to ±0.5° C. The diodes were irradiated with ^{60}Co gamma radiation with an exposure rate of about 10 R/min. The temperature range was 10° to 50° C, and the load resistance was varied between 1 MΩ and 10 kΩ.

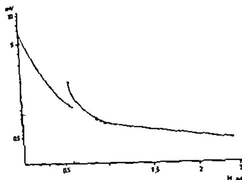


Fig 5 Radiation damage effect at ^{60}Co irradiation measured for a BPY 100 diode No 4

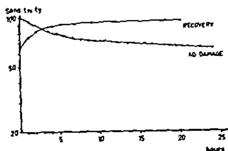


Fig 6 Loss of sensitivity as a function of the irradiation time for a Hoffmann s l con solar cell N 120 CG 9 and the recovery as a function of the time after finishing the irradiation

Sensitivity and radiation damage The initial sensitivity of the various diodes are shown in a Table The diodes were irradiated with a ^{60}Co beam with an exposure rate of 320 R/min It is well known that when the energy of the secondary electrons is sufficient ($>$250 keV) they can produce interstitial vacancy pairs (Frenkel defects) and other changes in the silicon and thus change the sensitivity of the diode These defects can produce donor and acceptor energy levels within the energy gap The effect is however more complex than that (DEARNALEY 1964) Several investigations on these effects in p n junctions have been reported (WHELPTON & WATSON 1963 ROSENZWEIG 1962)

To investigate the radiation damage effect for ^{60}Co radiation 5 BPY 11 diodes and 5 BPY 100 diodes were mounted on a perspex plate and irradiated simultaneously at 320 P/min In the Table the D_{50} doses obtained are indicated i e the doses which reduce the sensitivity to 50 % of the initial sensitivity The irradiations were performed in two sessions and the signals were measured with a load resistance of 1 MΩ The diodes were irradiated in the first session for 28 hours and after an interval of 96 hours they were irradiated again for 47 5 hours

An example of the curve for one of the diodes is given in Fig 5 As will be seen from the figure the sensitivity of the diode increased during the period without irradiation In all the ten figures obtained it was obvious that the curve after the interval could be connected to the extrapolated first part of the curve

One of the diodes was connected to a pen recorder and the effect of the interruption of the irradiation when the connection of the various diodes

Table

The initial sensitivity of the diodes measured with 1 MΩ in load resistance — The D_{50} dose is the dose which causes 50 % loss in sensitivity

Diode type	Number	Initial sensitivity (μV/R/min) ^{60}Co	D_{50} M rad
Siemens BPY 11	1	53 1	0 37
	2	59 0	0 3?
	3	55 9	0 15
	4	41 1	0 26
	5	59 6	0 19
Siemens BPY 100	1	12 4	0 23
	2	16 2	0 24
	3	17 9	0 12
	4	19 3	0 16
	5	23 1	0 24
Hoffmann B 120 CG 9	1	36 0	0 52
Hoffmann N 120 CG 9	1	23 7	0 58

Depth dose measurements have been performed in a water phantom and compared with results obtained with a small ionization chamber (BENNER et coll 1959) This chamber is 3 mm in diameter, and its calibration factor decreases with increasing energy, a factor of 1 16 between ^{60}Co and roentgen radiation with HVL 0 1 mm Cu As may be seen from Fig 4, the agreement between the chamber and the diode for ^{60}Co irradiation is complete, and for the roentgen beam the maximum deviation between the chamber and diode is less than 3 % up to 20 cm depth The reason why the difference is so small in spite of the great energy dependence of the probe measured free in air (HERTZ & GREMMELMAIER 1960) is that the spectral distribution of primary and secondary radiation does not to any great extent change with depth

The penumbra of the ^{60}Co beam has been measured with the chamber and the diode A lead block 2 cm × 8 cm × 8 cm was inserted at the centre of the field, just outside the collimator of the apparatus, and the cross section of the beam was measured in the phantom The diode gave 8 % higher dose just below the lead block, as compared to the chamber These measurements indicate that the diode can be used for depth dose measurements in homogenous phantoms but when a considerable change in the spectral distribution of the radiation is suspected, the measurements may be influenced by the energy dependence of the silicone diode

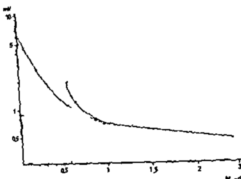


Fig 5 Radiation damage effect at Co irradiation measured for a BPY 100 diode No 4

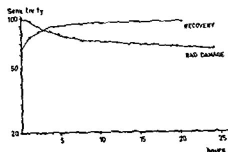


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Diode type	Number	Initial sensitivity (μV/R/min) ^{60}Co	D_{50} Mrad
Siemens BPY 11	1	53.1	0.37
	2	59.0	0.32
	3	55.9	0.15
	4	44.1	0.26
	5	59.6	0.19
Siemens BPY 100	1	12.4	0.23
	2	16.2	0.24
	3	17.9	0.12
	4	19.3	0.16
	5	23.1	0.24
Hoffmann B 120 CG 9	1	36.0	0.52
Hoffmann N 120 CG 9	1	23.7	0.58

Depth dose measurements have been performed in a water phantom and compared with results obtained with a small ionization chamber (BENNER et coll. 1959). This chamber is 3 mm in diameter, and its calibration factor decreases with increasing energy, a factor of 1.16 between ^{60}Co and roentgen radiation with HVL 0.1 mm Cu. As may be seen from Fig. 4, the agreement between the chamber and the diode for ^{60}Co irradiation is complete, and for the roentgen beam the maximum deviation between the chamber and diode is less than 3 % up to 20 cm depth. The reason why the difference is so small in spite of the great energy dependence of the probe measured free in air (HERTZ & GREMMELMAIER 1960) is that the spectral distribution of primary and secondary radiation does not to any great extent change with depth.

The penumbra of the ^{60}Co beam has been measured with the chamber and the diode. A lead block 2 cm × 8 cm × 8 cm was inserted at the centre of the field, just outside the collimator of the apparatus, and the cross section of the beam was measured in the phantom. The diode gave 8 % higher dose just below the lead block, as compared to the chamber. These measurements indicate that the diode can be used for depth dose measurements in homogenous phantoms but when a considerable change in the spectral distribution of the radiation is suspected, the measurements may be influenced by the energy dependence of the silicone diode.

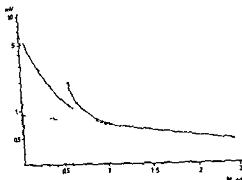


Fig 5 Radiation damage effect at Co irradiation measured for a BPY 100 diode No 4

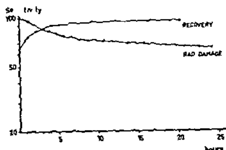


Fig 6 Loss of sensitivity as a function of the irradiation time for a Hoffmann silicon solar cell N 120 CG 9 and the recovery as a function of the time after finishing the irradiation

Sensitivity and radiation damage The initial sensitivity of the various diodes are shown in a Table The diodes were irradiated with a ^{60}Co beam with an exposure rate of 320 R/min It is well known that when the energy of the secondary electrons is sufficient (>250 keV) they can produce interstitial vacancy pairs (Frenkel defects) and other changes in the silicon and thus change the sensitivity of the diode These defects can produce donor and acceptor energy levels within the energy gap The effect is however more complex than that (DEARNALEY 1964) Several investigations on these effects in p n junctions have been reported (WHELPTON & WATSON 1963 ROSENZWEIG 1962)

To investigate the radiation damage effect for ^{60}Co radiation 5 BPY 11 diodes and 5 BPY 100 diodes were mounted on a perspex plate and irradiated simultaneously at 320 R/min In the Table the D_{50} doses obtained are indicated i e the doses which reduce the sensitivity to 50 % of the initial sensitivity The irradiations were performed in two sessions, and the signals were measured with a load resistance of 1 MΩ The diodes were irradiated in the first session for 28 hours and after an interval of 96 hours they were irradiated again for 47 5 hours

An example of the curve for one of the diodes is given in Fig 5 As will be seen from the figure the sensitivity of the diode increased during the period without irradiation In all the ten figures obtained it was obvious that the curve after the interval could be connected to the extrapolated first part of the curve

One of the diodes was connected to a pen recorder and the effect of the interruption of the irradiation when the connection of the various diodes

to the voltmeter was made, could be studied. A 45 min interval in the irradiation, for instance, with the same exposure rate, gave an increase in voltage from 3.25 to 3.30 mV. This increase had however disappeared after 6 min of irradiation, and the curve coincided with the extrapolation of the initial curve. The curves for the diodes seem to be divided in two exponential components, a rapid one and a slower one, as indicated in the figure. The doses seem to be too small, however, to enable a more accurate analysis of these phenomena.

The two Hoffman solar cells were also irradiated, and they showed more resistance to radiation damage than the BPY 11 and BPY 100 diodes, as may be seen from the Table. The diode named radiation resistant showed a slight increase in sensitivity (3 %) after 60 000 rad. The D_{50} for the Hoffmann diodes was found to be the same as for the International Rectifier diode (D_{50} = 500 000 rad) measured by WHELPTON & WATSON (1963).

To study the effect of fractionation of the dose, a N 120 CG 9 diode was irradiated with a total dose of 228 000 rad at 200 R/min, fractionated with intervals of 10 min irradiation and 20 min pause. This dose decreased the sensitivity by 14 %. For the N 120 CG 9 diode in the Table, the corresponding decrease in sensitivity for the same exposure was 20 %.

The effect of recovery was investigated with a N 120 CG 9 diode, and the result is plotted in Fig. 6. The diode was connected to the voltmeter and a pen recorder, and was irradiated to a loss in sensitivity of 36 % at an exposure rate of 720 R/min. After the irradiation, the cobalt apparatus and the recorder were automatically triggered for 15 seconds at certain intervals in order to get a signal from the diode. As will be seen from the figure, the diode sensitivity recovered *from 64 % to 94 % after 20 hours. Some defects produced in the* silicon crystal are stable at room temperature but the diode can recover on annealing (MOODY et coll. 1958, BEMSKI & AUGUSTYNIAK 1957). It may be observed that the recovery at room temperature does not seem to be 100 %.

Conclusions

It may be concluded that the use of the commercial diodes studied in this investigation should be restricted unless the parameters investigated can be kept under control. The temperature effect can be controlled either by measuring the temperature, for instance with a termistor, or by measuring the short circuit current, making the diode independent of temperature and exposure rate but less sensitive. *The energy dependence is not observable, for instance* when determining depth dose curves in a homogenous phantom with ^{60}Co,

but care must be taken when the spectral distribution varies so much that the energy dependence may influence the measurement

The most serious effect is the radiation damage which influences the reproducibility of the diodes The measurements performed have shown this phenomenon to be a complex one Radiation damage occurs also with the LiF dosimeter (MARRONE & ATTIX 1964) The sensitivity is good enough to make the diodes suitable for measurement of doses from an ordinary ^{60}Co apparatus used in the clinic Exposure rates may be measured at least down to 1 R/min The lithium drifted diodes investigated by BAILY & KRAMER (1964) seem to be more sensitive however than the photodiodes used in the present investigation

SUMMARY

Some commercial photodiodes have been tested for use in clinical dosimetry The following parameters were investigated sensitivity exposure rate dependence temperature dependence energy dependence and radiation damag The most serious disadvantage was *the radiation* damage effect which influences the sensitivity

ZUSAMMENFASSUNG

Kommerzielle Photodioden wurden mit Hinsicht auf die Verwendung in der klinischen *Dosimetrie geprüft Die* folgenden Parameter wurden studiert Sensitivität Abhängigkeit von der Dosisleistung Temperatur und Energie Abhängigkeit und Bestrahlungsschaden Der letztgenannt Effekt war der grosste Nachteil da die Sensitivität dabei beeinflusst wird

RÉSUMÉ

Les auteurs ont expérimenté *pour la* dosimetrie clinique des photodiodes du commerce Les paramètres étudiés sont la s nsibilité la dépendance à l égard du débit de dose de la température de l énergie et leur détérioration par les radiations Le plus sérieux inconvénient est leur détérioration *par les radiations* que influe sur leur sensibilité

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BENNER S RANSHULT J and GEBERT G Miniature ionization chambers for measurements in body cavities Phys in Med Biol 4 (1959) 26

to the voltmeter was made, could be studied A 45 min interval in the irradiation, for instance, with the same exposure rate, gave an increase in voltage from 3 25 to 3 30 mV This increase had however disappeared after 6 min of irradiation, and the curve coincided with the extrapolation of the initial curve The curves for the diodes seem to be divided in two exponential components, a rapid one and a slower one, as indicated in the figure The doses seem to be too small, however, to enable a more accurate analysis of these phenomena

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FROM THE INSTITUTE OF RADIOPHYSICS (DIRECTOR PROF R WALSTAM), KAROLINSKA SJUKHUSET STOCKHOLM SWEDEN

RADIATION PROTECTION MEASUREMENTS FOR A 17 MeV BETATRON

by

P E ÅSARD

This paper presents the results of measurements of the radiation milieu around a Siemens 17 MeV betatron (GUND & BERGER 1953) for clinical use Radiation protection measurements for this type of betatron have previously been reported by POHLIT (1961) BREITLING & SEEGER (1962) and VETTORI & PIGORINI (1963) The unwanted radiation produced outside the primary beam consists of three components roentgen rays electrons (negatrons and positrons) and neutrons Roentgen rays are generated when electrons are de celerated in filters target collimator doughnut and magnet The electrons come from photoelectric, Compton and pair production processes in the parts of the betatron mentioned above and from electrons having sufficient energy to leave the doughnut and the shielding of the betatron

Fast neutrons are produced by photonuclear and electro disintegrating processes especially in the lead collimator and the beam flattening filter For neutron production in high Z materials a threshold energy exists for the roent gen rays or the electrons, and this is as a rule larger than 6—8 MeV The neutron yield is less by a factor of approximately 1/137 (BROWN & WILSON 1954) for electrons compared to roentgen rays The greatest neutron intensity

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Table 1

Measurements in broad beam geometry of the electronic equilibrium conditions in a double chamber irradiated with ^{60}Co — Exposure rate 7 6 mR/min

Perspex cover mm	Exposure mR	Response in %
0	104	100
1 5		97 7
3 2		97 0
4 5		97 4
6 0		97 4
8 2		95 7

Table 2

Measurements of the electronic equilibrium conditions in a double chamber irradiated with stray radiation from the betatron — Primary beam 16 MeV electrons

Perspex cover mm	Response 0 mm perspex / Response d mm perspex
1	1 00
2	1 08
4	1 08

is found in the primary roentgen ray beam, where they are produced in the beam flattening filter and the lead collimator (LAUGHLIN 1951, HOFMANN 1955) The threshold energy for neutron production is for ^{204}Pb (γ,n) 8 2 MeV, for ^{207}Pb (γ,n) 6 8 MeV and about 7 4 MeV for ^{208}Pb (γ,n) with the resonance energy at about 14 MeV (GORYACHEV 1964)

Measuring techniques The so called double chambers (WALSTAM 1965) have been used for the measurement of roentgen rays and electrons The range is 10 to 200 mR for the outer chamber and 200 to 2 000 mR for the inner chamber when using the ordinary charging potential of 90 volt The chambers in PVC plastic containers, with 0 7 mm thick walls, have been calibrated free in air with a ^{60}Co source mounted in a lead collimator The exposure rate at a distance of 1 m from the source was 7 6 mR/min To estimate the wall thickness required to give electronic equilibrium conditions a chamber was placed in perspex containers with walls of different thicknesses As will be seen

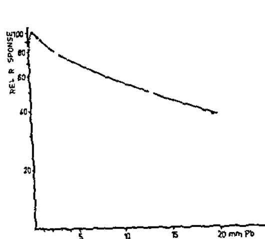


Fig 1 The relative respon e of a double chamber en closed in lead containers of d fferent wall thicknesses Pr nary beam 15 MeV electrons

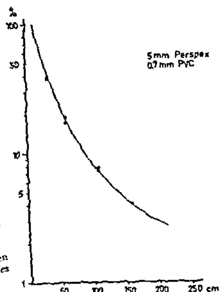


Fig 2 (ight diagram) Relative dose rates of stray radiation at different distances from the betatron head with double chambers enclosed in different containers The measurements were made along a line in the hori ontal plane through the betatron h ad and the plane of the doughnut (in the direc tion towards the right wall as seen in fig 6)

from Table 1 *no increase* in response due to electronic build up could be demonstrated This is in good agreement with the results reported by WALSTAM (1965) for chambers exposed in broad beam geometry For the measurements in the betatron 20 chambers showing the same calibration factor within ± 5 % were chosen

Measurements free in air of the electronic equilibrium condition were also performed outside the primary beam of the betatron at 16 0 MeV electron irradiation with a chamber placed 1 5 m from the head of the betatron As will be seen from Table 2 no increase in response with increasing wall thickness indicating electronic build up could be demonstrated This is due to the heterogeneity of the radiation and the irradiation geometry When the chamber was placed in different containers of lead however a small increase in the response of the chamber with increasing wall thickness was found (Fig 1) In these me isurements the primary beam was 15 MeV electrons and the chamber was placed 5 cm from the head of the betatron

As the chambers were intended to be used for dose distribution measurements of the stray radiation in the treatment room measurements were performed with chambers at different points in the treatment room with the thin PVC

Table 1

Measurements in broad beam geometry of the electronic equilibrium conditions in a double chamber irradiated with ^{60}Co — Exposure rate 7.6 mR/min

Perspex cover mm	Exposure mR	Response in %
0	104	100
1.5		97.7
3.2		97.0
4.5		97.4
6.0		97.4
8.2		95.7

Table 2

Measurements of the electronic equilibrium conditions in a double chamber irradiated with stray radiation from the betatron — Primary beam 16 MeV electrons

Perspex cover mm	Response 0 mm perspex / Response d mm perspex
1	1.00
2	1.08
4	1.08

is found in the primary roentgen ray beam, where they are produced in the beam flattening filter and the lead collimator (LAUGHLIN 1951, HOFMANN 1955). The threshold energy for neutron production is for ^{206}Pb (γ,n) 8.2 MeV, for ^{207}Pb (γ,n) 6.8 MeV, and about 7.4 MeV for ^{208}Pb (γ,n) with the resonance energy at about 14 MeV (GORYACHEV 1964).

Measuring techniques. The so-called double chambers (WALSTAM 1965) have been used for the measurement of roentgen rays and electrons. The range is 10 to 200 mR for the outer chamber and 200 to 2 000 mR for the inner chamber when using the ordinary charging potential of 90 volt. The chambers in PVC plastic containers, with 0.7 mm thick walls, have been calibrated free in air with a ^{60}Co source mounted in a lead collimator. The exposure rate at a distance of 1 m from the source was 7.6 mR/min. To estimate the wall thickness required to give electronic equilibrium conditions a chamber was placed in perspex containers with walls of different thicknesses. As will be seen

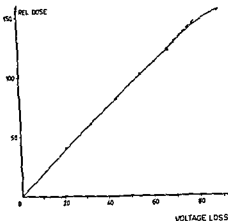


Fig. 3. Response of the inner chamber for stray radiation at a dose rate of 5 800 rad/min

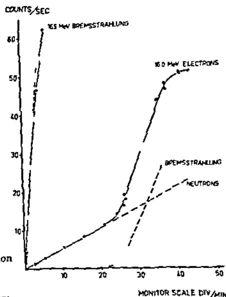


Fig. 4 (right diagram). Measurements with the rem counter just outside the door to the treatment room. Primary beam 16.5 MV roentgen rays and 16 MeV electrons. Monitor scale divisions/min is the relative dose rate in the primary beam

corresponding to discharges from 10 to 90 volt, and it can be seen from Fig. 2 that the recombination loss became apparent when the rest potential was less than 30 to 20 volt.

The radiation around a betatron is complex, and the R unit cannot be used in the measurements partly because of the electron contamination and partly because of the high energy of the roentgen rays. The dose rate in rad/min in water could have been used if the spectra of the electrons and the electromagnetic radiation were known. This is not the case and the appropriate stopping powers are thus unknown. For that reason the unit used in the measurements with the chambers was rad/min in air. Phantom measurements have been performed in cases where a more accurate estimate of doses outside the primary beam was needed for a patient. In calculating rad/min in air, the approximation has been made that the constants R/volt from the ^{60}Co calibrations were used in the measurements for the betatron. This may be expressed

$$D_{W} = 0.87\ \Delta V\ (Q/\text{volt}) \sim 0.87\ \Delta V\ (\text{R/volt})_{^{60}\text{Co}}\ \text{rad}$$

where ΔV = voltage discharge and Q = esu/0.001293 g air.

The outer chambers have never been discharged to less than 40 volt in order to eliminate recombination losses.

Table 3

Response of the outer chamber with stray radiation from the betatron at a dose rate of 85 mrad/min

Charging voltage voltage	Chamber 581	Chamber 582
	Response 90 V / Response V	Response 90 V / Response V
90	1 00	1 00
60	1 07	1 01
40	1 22	1 17

plastic containers and with perspex containers of 0 5 cm wall thickness An example of the results is shown in Fig 2 The chambers were placed at different distances from the betatron head and exposed to the stray radiation with 16 MeV electrons as primary beam As will be seen from Fig 2, the relative response between chambers in perspex containers and in PVC containers is practically the same regardless of the distance from the betatron In the measuring points at 160 and 210 cm from the betatron the response in chambers placed in PVC containers were 8 to 9 % higher, as compared to chambers in the perspex containers This is probably due to scatter from the walls, absorbed in the perspex containers but not in the PVC containers The differences obtained were so small that they may be neglected for the measurements of the dose distributions in the treatment room, and therefore in all the measurements reported below chambers with PVC containers have been used

Measurements of the recombination losses have been performed in both the outer and the inner chamber, the results are shown in Table 3 and Fig 3, respectively In the measurements of the recombination in the outer chamber, four chambers were placed 1 5 m from the betatron head The dose rate was 85 mrad/min in air with 16 MeV electrons as primary beam Two double chambers were charged at each measurement with 90 volt, and the charge voltage in the other two chambers was varied as is shown in Table 3 The dose was constant and corresponded to a decrease in voltage from 90 to 60 volt The measured recombination was larger than could be expected from theoretical estimations (WALSTAM 1965) These estimates did not, however, take into account the inhomogeneities of the electric field in the chambers

The recombination in the inner chamber was investigated by exposing a chamber charged to 90 volt in contact with the betatron head where the dose rate was 5 800 mrad/min The chamber was irradiated with different doses

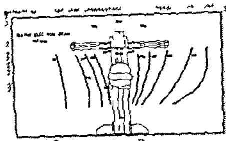


Fig 7 Dose rate distribution in a vertical plane through the betatron head Dose rate in the primary beam (16 MeV electrons) 200 rad/min

Bremsstrahlung intensity reaches such a level with this intensity in the electron beam that it gives detectable counts in the BF_3 counter The intensity from the roentgen rays in the proportional counter at 20 scale divisions/min on the betatron monitor was equal to about 110 mR/hr This corresponds to a mean exposure rate during the betatron pulse of 140 R/hr The reason why the roentgen ray component did not influence the counter at maximal output (about 7 scale divisions/min) with the 16 5 MV roentgen beam is that the exposure rate in the rem counter was some 7 times less in that case than in the case of the maximal output with the 16 0 MeV electron beam (corresponding to about 44 scale divisions/min)

The curve for 16 0 MeV electrons seems to become constant at higher exposure rates independent of the intensity of the primary beam This depends on the fact that the counts produced by the roentgen rays block the counter for the neutrons The counting rate is not however exactly 50 counts/sec but a little higher The explanation is that neutrons reaching the proportional counter more than 20 μsec after the leading edge of the betatron pulse then give counts because the counter is not blocked At higher neutron dose rates the plateau would occur at a greater height This was investigated by irradiating the rem counter with the same primary electron beam first with the counter in contact with the betatron head and then with the counter placed inside the treatment room at the right wall In the first case 89 counts/sec were observed at dose rates larger than 20 scale divisions/min and in the second case 57 counts/sec The rem counter was not used for dose distribution measurements in the treatment room because of the errors caused by the high intensities of the roentgen rays

Results

Measurements in the treatment room The dose distribution in the treatment room was measured for the 16 5 MV roentgen beam, filter 2, collimator B2, field size 5 9 cm diameter at FSD = 50 cm and with the 16 0 MeV electron

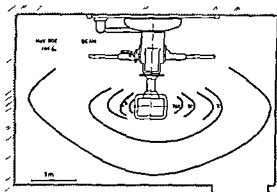


Fig. 5. Dose rate distributions of the stray radiation in a horizontal plane through the betatron head. Dose rate in primary beam (16.5 MV roentgen rays) 27 rad/min at FSD = 50 cm.

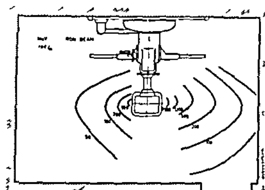


Fig. 6. Dose rate distribution in a horizontal plane through the betatron head. Dose rate in the primary beam (16 MeV electrons) 200 rad/min.

For the measurements of neutrons, a rem counter (ANDERSON & BRAUN 1964) from AB Atomenergi (Studsvik, Sweden) has been used. This rem counter has a dose response between neutron energies of 0.025 eV to 10 MeV which follows the ICRP (1955) rem response curve. The detector consists of a BF_3 proportional counter embedded in a moderator of polyethylene and boron plastic. A dose rate of 1 mrem/hr gives 2.4 pulses/sec with a pulse length of 20 μsec. The dose rate can also be read on a logarithmic ratemeter from 0.1 to 100 *mrem/hr*.

To test the linearity of the instrument with pulsed radiation it was placed just outside the door to the treatment room (Fig. 8), and the number of pulses per sec were measured as a function of the relative dose rate in the primary beam at 16.5 MV roentgen radiation and 16.0 MeV electrons. The results of the measurements are shown in Fig. 4.

The response of the rem counter when the primary beam was 16.5 MV roentgen radiation, showed a nonlinearity at counting rates larger than 30 counts/sec, that is, equivalent to 12.5 mrem/hr. The mean dose rate during the pulse (~5 μsec in length, 50 pulses/sec) was however much larger, namely 5 · 10^4 *mrem/hr*. This finding is in agreement with the data sheet of the rem counter, for which 10^4 pulses/sec are given as an upper limit for the instrument.

In the measurements with 16.0 MeV electrons as the primary beam there was a break in the curve at 20 scale divisions/min on the betatron monitor, as seen in the figure. (For these measurements, the chamber was in the same position outside the door.) The explanation of this phenomenon is that the

Table 4

Dose rate just outside door to treatment room as a function of the energy of the primary electron beam — Same filter and field size at all energies

MeV	mrad/min	mrad/krad
6	1 2	7 5
9	1 7	7 7
12	3 7	10 2
16	5 0	13 5

* mrad/krad means the dose at the measuring point per krad in primary beam

at point B, Fig 5, with 16 5 MV roentgen beam and a treatment distance of 50 cm is shown in Table 6 It is evident from these measurements that filter and field size had a negligible effect on the dose rate at point B There was no primary beam

Measurements of doses to patients In some cases it can be useful to know the dose to the patient outside the primary beam especially to certain organs This is particularly important when the patient is of fertile age

A technique for electron irradiation of retinoblastoma in children has been developed at Radiumhemmet (HULTBERG *et coll* 1965) The dose to the eye not intended to be irradiated has been measured with a chamber covered with 2 mm perspex placed in a phantom The result was that the lens received 6 to 7 rad per krad given to the other eye Doses to the gonad and testicle have also been measured, giving 60 to 80 mrad per krad A slight increase in the doses of about 10 % was found when the phantom was placed parallel with the plane of the doughnut

Measurements in the control room The dose rates from neutrons were measured at points 1 5 m above the floor Just outside the door, which is insufficiently protective the neutron dose rate with the 16 5 MV roentgen beam was 20 mrem/hr (corrected for dead time losses in the rem counter) and with the 16 0 MeV electron beam it was 10 mrem/hr The dose rates at other points in the control room are given in Fig 8 The deflections of the neutrons in air and walls caused a higher dose rate at the opposite wall of the room than found in the vicinity of the wall of the treatment room The protection in this area will be improved

beam filter 6 (0.2 mm Pb), tube of 8 cm diameter. The dose rate in the primary beam was 27 rad/min at FSD = 50 cm and 200 rad/min, respectively. The chambers were placed on a wooden support and 20 were exposed simultaneously. A mix-D body phantom was placed on the treatment couch in all the measurements. The results are given in Figs. 5 to 7.

In the place of the doughnut the intensity is at a maximum. The distribution is not symmetrical around the betatron head in the case of 16 MeV electrons as primary beam. *The intensity has a maximum on that side in the plane of* the doughnut where the primary beam is taken out, and is 4 to 6 times higher than the dose rate on the other side. The reason for the high intensity is that only about 4 % of the electrons present in the doughnut during the acceleration are present in the primary beam. The rest of the electrons are lost producing ionization and roentgen radiation. About 50 % of the electrons which hit the anticathode are lost (GUND & SCHITTENHELM 1953).

A high intensity was also found in the direction opposite to the primary beam. The magnet does not absorb the radiation produced in that direction. VETTORI & PIGORINI (1963), for the same type of apparatus, reported a maximum in the vicinity of the injector. These authors also divided the stray radiation into soft (mainly electrons) and hard components. The soft component of the stray radiation of a 15 MeV primary electron beam is totally absorbed after ~ 4 g/cm². The half value layer of the hard component was found by measurement to be 13 mm Pb. This value is in good agreement with the measurements recorded in Fig. 1, showing that 12 mm Pb causes a 50 % reduction of the maximum intensity. These measurements are not directly comparable, however, because of the different geometries.

The dose rate just outside the door to the treatment room, as a function of the energy of the primary electron beam when using filter 5 (0.1 mm Pb) and a tube of 5 cm diameter, is shown in Table 4. In this table, mrad/krad means the dose at the measuring point when a maximum dose of 1 krad is given to the patient.

The ratio mrad/krad is strongly dependent on which filter is used, as may be seen from Table 5. These measurements were performed at point A, Fig. 7, with the 16 MeV electron beam. The dose rate at point A is practically independent of filter and field size, but the dose per krad varies with a factor 6 to 7 between filter 0 and filter 8. A thicker filter results namely in a larger decrease in dose rate for the primary beam, and thus a longer time is needed for any given dose to the patient, while the intensity of the stray radiation depends on the fact that only a small and fairly constant fraction of the accelerated electrons actually reach the primary beam, independent of the filter used.

The dependence *of beam flattening filters and field sizes on the dose rate*

Table 4

Dose rate just outside door to treatment room as a function of the energy of the primary electron beam — Same filter and field size at all energies

MeV	mrad/min	mrad/krad
6	1 [illegible]	7 5
9	1 7	7 7
12	3 7	10 2
16	5 0	13 5

* mrad/krad means the dose at the measuring point per krad in primary beam

at point B Fig 5 with 16 5 MV roentgen beam and a treatment distance of 50 cm is shown in Table 6 It is evident from these measurements that filter and field size had a negligible effect on the dose rate at point B There was no primary beam

Measurements of doses to patients In some cases it can be useful to know the dose to the patient outside the primary beam *especially to certain organs* This is particularly important when the patient is of fertile age

A technique for electron irradiation of retinoblastoma in children has been developed at Radiumhemmet (HULTBERG et coll 1965) The dose to the eye not intended to be irradiated has been measured with a chamber covered with 2 mm perspex placed in a phantom The result was that the lens received 6 to 7 rad per krad given to the other eye Doses to the gonad and testicle have also been measured giving 60 to 80 mrad per krad A slight increase in the doses of about 10 % was found when the phantom was placed parallel with the plane of the doughnut

Measurements in the control room The dose rates from neutrons were measured at points 1 5 m above the floor Just outside the door which is insufficiently protective the neutron dose rate with the 16 5 MV *roentgen beam* was 20 mrem/hr (corrected for dead time losses in the rem counter), and with the 16 0 MeV electron beam it was 10 mrem/hr The dose rates at other points in the control room are given in Fig 8 The deflections of the neutrons in air and walls caused a higher dose rate at the opposite wall of the room than found in the vicinity of the wall of the treatment room The protection in this area will be improved

beam filter 6 (0 2 mm Pb), tube of 8 cm diameter The dose rate in the primary beam was 27 rad/min at FSD = 50 cm and 200 rad/min, respectively The chambers were placed on a wooden support and 20 were exposed simultaneously A mix D body phantom was placed on the treatment couch in all the measurements The results are given in Figs 5 to 7

In the place of the doughnut the intensity is at a maximum The distribution is not symmetrical around the betatron head in the case of 16 MeV electrons as primary beam The intensity has a maximum on that side in the plane of the doughnut where the primary beam is taken out, and is 4 to 6 times higher than the dose rate on the other side The reason for the high intensity is that only about ¼ % of the electrons present in the doughnut during the acceleration are present in the primary beam The rest of the electrons are lost producing ionization and roentgen radiation About 50 % of the electrons which hit the anticathode are lost (GUND & SCHITTENHELM 1953)

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The dependence of beam flattening filters and field sizes on the dose rate

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Table 5

The dependence of filters and field sizes on the dose rate at point A (Fig 7) — Primary beam 16 MeV electrons

Filter	Tube cm diam	mrad/min	mrad/krad*
0	8	111	130
4 (3 10^{-2}/mm Au)	8	108	190
8 (0 6 mm Pb)	8	120	850
8	3	112	580

* mrad/krad means the dose in point A par krad in primary beam

Table 6

The dependence of beam flattening filters on the dose rate at point B (Fig 5) — Primary beam 16 5 MV roentgen rays

Filter	Collimator	mrad/min	mrad/krad
0	B 2	57	—
2	B 2	62	1300
3	B 2	60	1500
0	Collimator closed	58	—

* mrad/krad means the dose in point B per krad in the primary beam

Discussion

It may be noted on the basis of these measurements that even if the dose rate from the stray radiation may be as much as 10 times larger with 16 0 MeV electrons, compared to the dose rate with 16 5 MV roentgen irradiation, the dose outside the beam per rad in the primary beam may be about the same With small field sizes, when a thin filter can be used for the electron beam, the dose from stray radiation per rad in the primary beam is generally less compared with the roentgen beam

In the measurements around the betatron, differences in dose rates in different directions from the betatron head were estimated, these can have some economic consequences in the calculation of thicknesses of walls and roof and with respect to the position of the betatron in the treatment room POHLIT (1961) has pointed out that the distribution of roentgen radiation around the betatron is not influenced to any great extent by the size of the room, and measurements can therefore be generalized This does not apply to neutrons,

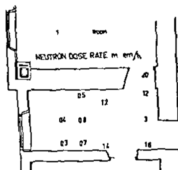


Fig 8 Dose rate from fast neutrons in the control room adjacent to the treatment room Dose rate in primary beam (16 5 MV Bremsstrahlung) 27 rad/min at FSD = 50 cm

however The doses to patients outside the primary beam seem to be negligible in the cases investigated This applies also to the higher energies available on our betatron (VETTORI & PIGORINI 1963) AZUMA (1963) has measured the contamination of electrons in a 17 MeV roentgen beam from a Siemens betatron and pointed out that the eyes can be protected from the electrons by an absorber 5 g/cm thick

The qualities of the rem counter can be improved for use with pulsating irradiation for instance by decreasing the dead time and thus enabling higher dose rates to be measured The level of the discriminator can also be changed thereby making it possible to some extent to discriminate pulses produced by the roentgen radiation (LYDEN 1965)

SUMMARY

The dose distribution from stray radiation around a Siemens 17 MeV betatron was measured and the dependence on radiation type energy filters and field size and doses to critical organs using a special irradiation technique have been studied Doses from neutrons in an adjacent room and the suitability of the instrument used in pulsating beams were studied with a rem counter

ZUSAMMENFASSUNG

Die Dosisverteilung der Streustrahlung um einen Siemens 17 MeV Betatron wurde bestimmt Die Abhängigkeit von Bestrahlungsart Energie Filter und Feldgrosse mit Hinsicht auf die Dosis fur strahlensensible Organe wurde mittels einer speziellen Bestrahlungstechnik untersucht Die Neutronendosis von einem naheliegendem Zimmer wurde mit einem rem Zahler gemessen und die Verwendbarkeit dieses Instrumentes wenn in einem pulsierenden Strahlenbundel verwendet wurde studiert

RÉSUMÉ

La distribution de dose du rayonnement diffusé autour d un bétatron Siemens de 17 MeV a été mesurée L auteur a mesuré la dépendance de cette distribution de dose à l égard du type d irradiation, de l énergie du filtre et des dimensions du champ ainsi que les doses aux organes critiques avec une technique spéciale d irradiation Il a étudié avec un compteur rem les doses dues aux neutrons dans la piece adjacente et la fiabilité de cet instrument dans les rayonnements pulsés

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FROM THE RADIOTHERAPY CLINIC (DIRECTOR PROF S MUSTAKALLIO), OF THE UNIVERSITY CENTRAL HOSPITAL OF HELSINKI, FINLAND

PRODUCTION OF ^{18}F FOR BONE SCANNING

by

LAURI PATOMÄKI

The first application of ^{18}F to biologic work was made in 1940 but the use of the isotope was rendered difficult by the fact that only small activities could be produced (BERNSTEIN & KATZ 1953) It was later observed (KNIGHT NOVEY CANNON & TURKEVICH 1951) that ^{18}F could be produced in a thermal reactor by the irradiation of a compound containing both lithium and oxygen Since then the production of quite large activities on an economic basis has been easy

If no commercial radiochemical processing laboratories are near ^{18}F may be prepared on the spot provided a thermal reactor with a flux of the order of 10^1 n/s cm such as is frequently available in universities and training institutes lies within 20 km of the clinic The half life of only 110 min of ^{18}F may then possess few disadvantages The practical preparation of ^{18}F in the normal isotope laboratory of a radiotherapy clinic was the aim of this work the isotope should be in a form suitable for in vivo studies particularly when it is required for oral administration in bone scanning

The production of ^{18}F A number of nuclear reactions result in the production of ^{18}F activity such as ^{18}O(p n)^{18}F in cyclotrons and reactors (CARLSON et coll 1959 NUSYNOWITZ et coll 1965) In thermal reactors production can be ef

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RÉSUMÉ

La distribution de dose du rayonnement diffusé autour d un bétatron Siemens de 17 MeV a été mesurée L auteur a mesuré la dépendance de cette distribution de dose à l égard du type d irradiation, de l énergie, du filtre et des dimensions du champ ainsi que les doses aux organes critiques avec une technique spéciale d irradiation Il a étudié avec un compteur *rem les doses dues aux neutrons dans la piece adjacente et la fiabilité de cet instrument dans* les rayonnements pulsés

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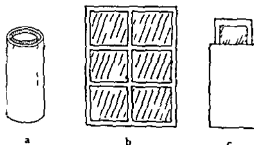


Fig 2 Forms of sample packages used in the neutron irradiation a) Cylindrical sample made of plastics b) Flat sample made of plastics c) Sample of aluminium Shaded areas refer to Li_2CO_3

then precipitated The phosphate is filtered off in a glass filter (5 to 15 microns) and washed Tritium and lithium are thus separated from ^{18}F The phosphate is dissolved in 5 ml 2 7 normal (warmed) HCl in the filter Finally about 10 ml of concentrated Na_3 citrate is added for adjustment of the pH to about 4 The solution is now ready for oral use

This method differs slightly from the one described by ANBAR (1963)

The final solution usually carries an activity of 1 mCi of ^{18}F per 3 g of irradiated lithium carbonate From the moment the sample is taken out of the reactor 6 km from the clinic one hour has elapsed Chemical separation by the method described takes about 20 minutes The yield is usually about 80 % If the solution is to be used for intravenous injection it must be neutralized, and no citrate should be added (ANBAR 1963 DWORKIN et coll 1965 THOMAS et coll 1965)

Form and size of the sample during neutron irradiation The size of the lithium carbonate sample greatly influences the specific activity achieved at neutron irradiation by reason of the large cross section of ^6Li to thermal neutrons If the thickness of the sample should exceed 2 mm the specific activity will no longer rise (Fig 1) This means that the sample will be effectively irradiated only to a depth of 1 mm from the surface

The samples used have been either cylindrical (Fig 2a) or flat (Fig 2b) The boxes are made of a plastic material usually a thin plastic foil An aluminium envelope has also been employed (Fig 2c) This is however not practical as the aluminium is also activated and is accordingly difficult to handle Bags made of thin plastic foil seem to be the best choice since they will not be radioactive are easily cut open and may be discarded after use In these packages the thickness of lithium carbonate will not exceed 2 mm If enriched lithium (^6Li) is utilised the cross section of the carbonate will be more than ten times as large and therefore the thickness of the lithium carbonate should not exceed 0 2 mm

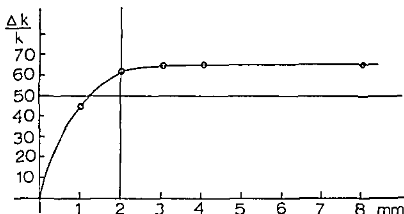


Fig 1 Effect of thickness of sample on the reactivity of the reactor and thus on the specific activity of the sample

fected by a chain reaction, at first $^{6}Li(n, {}^{4}He)\,{}^{3}H$ The resulting fast tritons ^{3}H will induce ^{18}F activity by $^{16}O({}^{3}H,n){}^{18}F$ (BERNSTEIN & KATZ 1953, KNIGHT et coll 1951) These two reactions are induced simply by setting some lithium salt containing oxygen in the neutron flux of a thermal reactor

BEG & BROWN (1963) utilised Li_2O for this production Their method is applicable for medical purposes if a modification is introduced in view of the high tritium content in the product However, in common with many others, we have made use of Li_2CO_3, irradiated at the Institute of Technology at Otaniemi in a Triga reactor with a maximum power of 100 kW If the ^{18}F is to be without chemical and radiochemical impurities, the sample needs some chemical purification after irradiation Known methods of distillation (ERICSSON 1961, THOMAS et coll 1965) could not be used for the separation of ^{18}F as at first the simple apparatus required for this purpose was not available Moreover the high tritium content associated with this method (THOMAS et coll) was considered undesirable Accordingly, with the method first applied we used AlO as an ion exchanger (STANG 1963) This procedure appeared too slow however at least with the chromatographic alumina at hand, wherefore the following method was thereafter employed

Three grams of irradiated Li_2CO_3 (two hours in 4 10^{1} n/s cm) are first dissolved in 30 ml 2 7 normal HCl The carbonate is released and therefore the process should be carried out under a fume hood and behind lead bricks to avoid radiation hazards The dose rate at 20 cm, without shielding, is about 20 mR/hour One millimole of H_3PO_4 is added together with 0 2 mM of a $CaCl_2$ solution The pH is adjusted to about 9 (or more) by the addition of 10 ml 2 5 normal NaOH Calcium phosphate, carrier of the main part of the ^{18}F activity, is

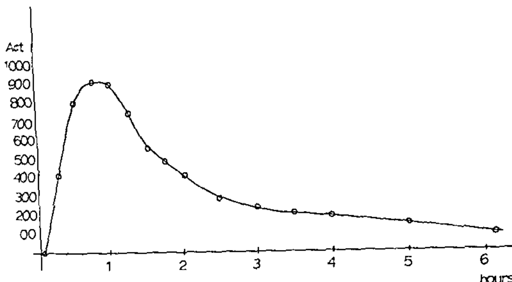


Fig 3 Blood excretion curve after an oral dose of carrier free ^{18}F fluoride

lithium It may be assumed that under certain conditions a single dose exerts no toxic effects but the amount could nevertheless be further reduced by a tenth by the use of isotopically enriched ^{6}Li lithium carbonate

The method of purification outlined above although not essential, has been applied because it is relatively quick and simple After purification only ^{18}F and ^{35}S isotopes are present in the final solution Measurements have indicated however that some contamination with ^{3}H will also be present about 1 μCi per 1 mCi of ^{18}F ingested and lithium has therefore also been separated in this way

Blood excretion curve and the use of ^{18}F The presence and disappearance of fluorine in the blood following its ingestion has been studied by taking blood samples within 6 hours of its oral administration (Fig 3) The disappearance attributable to radioactive disintegration has been corrected at each point so that the curve indicates only the fluorine flow to and from the blood stream After 6 hours no more than 10 % of the maximum amount of fluorine (at 1 hour) remained in the blood However it cannot be expected to be excreted to this extent (BLAU et coll 1962 Dworkin et coll 1965 NUSYNOWITZ et coll 1965) which means that the fluorine must be concentrated elsewhere in the body It is known (VAN DYKE et coll 1965 NUSYNOWITZ et coll) that fluorine con

Table 1

Activity present in an irradiated sample of 3 g Li_2CO_3

Isotope	Activity	
^{3}H	2 600	μCi
^{18}F	2 000	»
^{24}Na	1 0	»
^{38}Cl	2 0	»
^{36}Cl	0 03	»
^{35}S	0 003	»
^{42}K	0 003	»

Table 2

Radiation dose due to oral administration of 1 mCi ^{18}F at 30 minutes after irradiation with no purification of sample

Isotope	Activity (μCi)	Total body (mrad)	Bone (mrad)
^{3}H	1 600	120	120
^{18}F	1 000	30	230
^{24}Na	0 61	1 0	1 0
^{38}Cl	0 55	0 03	0 03
^{36}Cl	0 018	0 13	0 13
^{35}S	0 002	0 02	0 01
^{42}K	0 002	0 01	0 01
	Total	150 mrad	350 mrad

An increase in thickness entails a loss in the excess amount of the carbonate, without any gain of activity

Radioactive components of an irradiated Li_2CO_3 sample After irradiation and before purification, isotopes other than ^{18}F exist in the sample, dependent upon the presence of impurities in the irradiated carbonate The most important by product is naturally tritium Theoretically, there should be about 5 mCi of tritium to 3 g of Li_2CO_3, although in practice much less is obtained (Table 1) This indicates that the geometry of the sample concerned is not the best possible

Only ^{18}F and ^{24}Na peaks are detectable 24 hours after irradiation in the gamma spectrum of an irradiated sample ^{38}Cl, which has an initial activity of 2 μCi, has a half life of 37 minutes and thus completely vanishes 24 hours after irradiation (1 60 and 2 15 MeV gammas) ^{42}K has such a slight activity that it is not discernible in the spectrum ^{3}H, ^{35}S and ^{36}Cl have no gamma transitions

Radiation dose induced by different isotopes in the sample The dose to the patient caused by the activities present when one millicurie of ^{18}F is administered and the sample is not purified, is small (Table 2) Only fluorine and tritium produce an appreciable dose When tritium and other isotopes are separated from the fluorine, the radiation dose of ^{18}F per 1mCi will be reduced by 35 % in bone and by 80 % in the entire body In any event, the dose does not seem to be excessive, and for this reason the separation of tritium is not absolutely necessary The separation of lithium which is not radioactive has been considered essential (STANG & RICHARDS 1964) Three grams of lithium carbonate contain 0 57 g



Fig 4 Scintillation camera views from abdominal and pelvic areas demonstrating the flow of ^{18}F from stomach to spine a) At 5 min after the oral dose all the activity is still in the ventricle b) At 20 min the fluorine lies mainly in the intestine although the spine is already visible to the left c) At 50 min fluorine is seen in the middle of the lumbosacral area d) At 3 hours this is seen more clearly than in (c) The dots in (d) indicate the navel and processus ensiformis

centrates in bone (Fig 4) Fluorine has been used for two years for bone scanning in cases of primary or metastatic bone lesions and a report on these studies will be published

SUMMARY

A method of producing ^{18}F for scanning primary and metastatic bone lesions is described The ^{18}F may be prepared in the normal isotope laboratory of a clinic if the neutron irradiation can be effected at a laboratory within a distance of 20 km Impurities and their influence upon the radiation dose are discussed The behaviour of fluorine after its oral administration is considered

ZUSAMMENFASSUNG

Eine Methode zur Herstellung von ^{18}F fur Scanning bei primaren und metastatischen Knochentumoren wird angegeben ^{18}F kann in einem gewohnlichen klinischen Istotopenlaboratorium hergestellt werden falls die Neutronenbestrahlung bei einem Ort stattfinden kann der nicht mehr als 20 km vom Istotopenlaboratorium entfernt ist Beimischungen und deren Einfluss auf die Strahlendosen werden besprochen Was mit dem Fluor nach der oralen Verabreichung geschieht wird ebenso besprochen

RÉSUMÉ

L auteur decrit une methode de production de ^{18}F pour le diagnostic isotopique des lesions osseuses primitives et metastatiques Le ^{18}F peut etre prepare dans le laboratoire des isotopes normal d un hopital si l irradiation par les neutrons peut etre faite a une distance inferieure à 20 km L auteur etudie les impuretes et leur influence sur la dose d irradiation Il examine le devenir du fluor après son administration orale

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Book reviews

DOSIMETRIE ZUR BETATRONTHERAPIE Von Wolfgang Pohlit 80 Seiten 55 Abbildungen 7 Tabellen Georg Thieme Verlag Stuttgart 1965 Preis 25 DM

This little book deals with the different measurements of the source of radiation and of the electron and photon beams to secure correct treatment dosimetry These are of great topical interest in modern radiotherapy Clinical dosimetry, including dose planning and radiation protection also have their own chapters

Within the limited space available a good account is given of the instruments and measuring methods developed over a number of years at the Max Planck Institut fur Biophysik Frankfurt am Main A great number of practical hints on the performance of measurements and various sources of error and their avoidance are given as well as formulae and numerical data needed for converting the direct instrument readings into absolute dose values in rad The book will be most useful to hospital physicists working with medical betatrons or other high energy accelerators but may also be read with advantage by radiotherapists

Sten Benner

CURRENT TOPICS IN RADIATION RESEARCH Vol 2 Edit by M Ebert and A Howard 598 pages with 118 figures and 7 tables North Holland Publishers Company, Amsterdam 1966 Price 45 guilders

In the first volume of this series the trend was predominantly radiobiologic In the present volume some of the chapters are of a nature to demand of the reader some knowledge in physics and chemistry

The biologic macromolecules are targets of importance in the action of radiation on living matter and it is of value to find an exposé by HENGLEIN & SCHNABEL on the radiation effects of macromolecules in general The authors have worked with synthetic polymers and special attention has been paid to reactions in aqueous solutions rather than in the dry stage Degradation cross linking and gel formation of molecules as well as the effects of irradiation of varying LET s are discussed There seem to be great variations in regard to cross linking and gel formation between various polymers depending on whether γ radiation or particle radiation is used Energy transfer between water and dissolved polymers occur and free radicals such as OH and H atoms add to the effects

JUNG & ZIMMER introduce their chapter on Some chemical and biological effects of elastic nuclear collisions with the statement It may seem surprising to find a review article written on a topic which does not yet actually exist This means that up to now no direct evidence of elastic nuclear collisions has been given but the authors prove their existence and suggest that such reactions give rise to biologic effects When charged particles of high velocity are used ionization and excitation predominate and the likelihood that elastic nuclear collisons occur is very small However at very low ion velocities more energy is dissipated by elastic collisions than by interaction between incident ions and electrons of the exposed material Slow particles should therefore be used to prove the effect which nevertheless meets with diffi

culties because of their very low penetrative capacity in biologic material The authors discuss an elegant experimental solution of the problem by means of protons and thin layers of plastic foils in which the absorption spectra produced the evidence Work with the enzyme ribonuclease in thin layers also proved that elastic collisions between slow charged particles and this molecule caused an inactivation that increased linearly with the proton dose

The chapter by PHILLIPS on energy transport in carbohydrate is of biologic significance because of the abundance of such substance in the cells Already in the metabolic processes energy transfer occurs in steps although not well defined in physical terms A great number of molecules absorb light in the range of ultraviolet and visible and in biochemical processes this is followed by transfer of energy By the application of ionizing radiation the energy becomes considerably in excess of what can be used in the biologic process The ionizing radiation action is discussed in detail but cannot be dealt with at length in this review In particular two carbohydrates the d glucose and cycloamylose complexes are well analysed A chapter on the effects of ultraviolet light on photoreactivation (by JANE SETLOW) is motivated by the fact that ultraviolet has both lethal and mutagenic actions The changes caused in nucleic acids in particular are manifold and important The author discusses chain breaks and depolymerization cross linking and partial denaturation Specific reactions occur in several of the base components of the nucleic acids and DNA may loose its synthetic ability Ultraviolet lesions can be repaired as has been shown by many writers This photoreactivation is in many instances promoted by heat in which reaction an enzyme seems to take part The mechanism of ultraviolet induced mutations appears still not to be completely understood

JOSET MOUSTACCHI & MARCOVICH report on determinations of the initial sites of radiation effect on microorganisms essentially *Escherichia coli* and yeast cells Roentgen rays as well as ultraviolet rays are considered The problem is that it usually takes several generations to detect a lethal mutation Experiments were carried out by irradiating *F coli* K12 Hfr male cells (*Hfr* for high frequency of recombination) and mating them with non irradiated F recipient ones During conjugation between a Hfr donor and a F recipient the genetic determinants of the donor are transferred to the zygote sequentially and in an order that is constant for a given Hfr strain The frequency of transfer of a marker decreases as a function of its distance from the point of the chromosome first transferred the origin O One can thus define a gradient of transfer of the male characters and a degree of linkage between them expressed as their probability of being simultaneously transmitted to the recombinants The study of the variation of these two factors as a result of the irradiation of the male or of the female has been used as a tool to analyse the radio-induced lethal damage Any dominant lethal lesion induced on the male chromosome should have a lethal effect on the zygote

BRINKMAN & LAMBERTS report on several experiments of interest in radiation therapy The first example is on water filtration through the subepidermal layers of membranes The permeability is greatly increased by irradiation with such small doses as 1 to 2 R and the application of moderate water pressure This effect is counteracted by radiation protective compounds like SH groups and serotonin The experiments have some bearing upon the penetration of activity should the situation be such that heavy fall-out occurs Further enzymes may be rapidly released e g from erythrocytes by comparatively low doses It is reported that ozone in low concentration has radiation sensitizing effects as demonstrated by irradiation of mice given O_3 inhalations of about 1 part per million This treatment which has no deleterious effect as such increased the death rate considerably after a nearly lethal dose The authors suggest that it may be worthwhile to follow up the ozone effect more in detail

The last chapter by FOWLER on Radiation biology as applied to radiotherapy constitutes a discussion of great interest both to radiation biologists and therapists The experimental

material on survival curves of cells or cell populations has increased considerably in the last decades, as has information on the biochemical and other factors that settle the issue of the irradiation The author discusses cellular theories of radiosensitivity and variations due to factors such as in vivo or in vitro exposure, stage of mitotic cycle and degree of differentiation It is not easy to recommend definite clinical procedures He believes that the most important *aspects to deal with are the anoxic cells in tumours and to find rational ways of fractionation* It is generally known that radiation sensitivity increases when cells and tissues are well oxygen ated, and that in anoxia 2 to 3 times higher doses are needed for an equivalent damage The author also points to the fact that living tumour cells are situated around capillaries whereas tissue at some distance may be necrotic Tumour cells at the edge of necrotic regions may survive for some time however and because of the anoxic state also survive irradiation and eventually regrow One of the main problems in radiotherapy are these anoxic and conse quently resistant cells

FOWLER considers some of the possibilities in dealing with the problems The first of these is the application of high pressure oxygen during irradiation, as practised by Churchill Davidson and his team although many radiotherapists seem to be sceptical about this form of therapy However six centres in the UK at least two in USA and two in Australia are by now engaged in such treatment The second is the breathing of 95 % O_2 plus 5 % CO_2 at nor mal pressure to afford hyperventilation and capillary dilatation and the third is local infusion of H_2O_2 which should be followed by the reaction $2H_2O + O$ Lastly radiation at high ionizing density because it kills even anoxic cells almost as well as normal cells is mentioned

The last section is on dose fractionation in which the methods are discussed It seems impos sible to generalize or even to give preference to a particular schedule of fractionation at the present time The author states There is no a priori reason why any number of fractions *might be better than any other from 2 to 200 fractions or even continuous irradiation* This drastic statement can be rephrased to mean that each therapy problem must be approach ed in an individual way

Arne Forssberg

BIOPHYSIKALISCHE PROBLEME DER STRAHLENWIRKUNG Jahrestagung der Deutschen Gesell schaft fur Biophysik am 23/24 April 1965 in Homburg/Saar Herausgegeben von H Muth 191 Seiten mit 114 Abbildungen und 10 Tabellen Georg Thieme Verlag Stuttgart 1966 Preis 29 70 DM

This book of twenty six congress papers is introduced with a review of biophysics by B Rajewsky Some of the papers consider radiation dose calculations and the biologic actions of Thorotrast, ^{226}Ra and ^{1}Ra and their disintegration products while others deal with radiobiologic and radiochemical questions the reactions of free radicals and their detection by electron spin resonance radioprotective and mutagenic agents and the metabolism of ^{137}Cs The use of analogue computers in medical and biologic research is discussed in one paper In another paper it is pointed out that unwarranted conclusions regarding underlying mechanisms are often drawn from the shape of dose survival curves Finally the new bio physical institute at Homburg/Saar is described

The book should be *of great interest to all active in radiation biophysics* as it gives a good though necessarily somewhat disjointed account of the present state of the science as well as of work going on in West Germany The selection of the topics was of course determined by the contributors

Sven Benner

A C T A R A D I O L O G I C A

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TELEGAMMA THERAPY OF LARYNGEAL CARCINOMA

by

O DAHL F JACOBSSON and R WALSTAM

It is now generally agreed that high energy radiation is the most convenient means of treating laryngeal carcinoma (GOLDMAN & SILVERSTONE 1960 MORRISON & DEELEY 1962, and FLETCHER & KLEIN 1964) Various treatment units and techniques may then be advantageously applied

Gamma radiation has been used for this purpose at Radiumhemmet for about thirty years Teleradium units were employed until 1954 JACOBSSON (1951 1952) reported and analysed the 1935 to 1945 material of 178 patients with carcinoma of the larynx An intensified and more detailed individual dose planning was started in 1953 Decacurie cobalt 60 units were installed in 1954 and 1956 (LINDELL & WALSTAM 1956 DAHL LINDELL & WALSTAM 1956) these offer better possibilities to adapt the dose distribution to the position and size of the tumour and to the anatomical conditions From 1955 decacurie cobalt 60 was mainly used for this treatment and in recent years the simpler ordinary telecobalt therapy The short distance gamma beam irradiation technique is suitable chiefly for small tumours larger carcinomas or wide spread demand other techniques

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From Radiumhemmet (Acting Director F Jacobsson) and the Institute of Radiation Physics (Director R Walstam) Karolinska Sjukhuset Stockholm Sweden Submitted for publication 4 July 1967

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Fig 2 Roentgenogram of the treatment area with magnification indicator applied to the patient's skin

Two-dimensional dose planning is performed on an anatomical plan of the cross-section through the tumour centre as illustrated in Fig 3 The choice of beam nozzles and of the distance between and angulation of the central axes of the beams is made with due regard to the size and position of the tumour and to the possible compression of soft tissues In most patients a two-field technique with beam nozzles provided with special wedge filters has usually supplied a satisfactory dose distribution for small tumours The height of the field has been 3 4 or 6 cm However where regional metastases have been present other techniques have been used The aim has been to deliver a calculated dose of 5 600 rad in approx 2 to 3 weeks to small tumours and 6 000 rad in about 3 to 4 weeks o larger neoplasms The error of method in these dose figures has been estimated to be within + 5 and — 10 per cent The corresponding dose distribution in a sagittal section with a field height of 6 cm is given in Fig 4

In comparison with conventional roentgen rays the hard gamma radiation gives a diminished absorption and reaction in calcified cartilage and a skin sparing effect which may also be obtained with the closed-end treatment applicators that we have used (WALSTAM 1965)

Among the special advantages of the decacurie technique may be mentioned that both the overall treatment time and the duratoin of the tissue reactions are relatively short To avoid undue reactions it is of course necessary to base the dosage in the individual case on repeated clinical investigations during treatment

Optimal results with the decacurie technique demand that the whole staff be familiar with the technique and that the setting up for each treatment is care



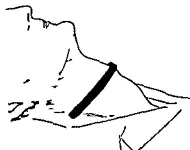




Fig 1 Illustration of the tracing of the anatomical outlines with the aid of a dental mould and preparation of a perspex jig

The main purpose of this paper is to present a material treated almost entirely with high energy radiation rather than to argue in favour of a special irradiation technique Preliminary reports were given by DAHL & WALSTAM (1957) and DAHL, JACOBSSON & WALSTAM (1964) The authors feel it necessary first to give a brief summary of the technique

The use of narrow beams from short distance gamma units with their rapid dose fall off necessitates a careful planning of the irradiation The first step in the preparation before irradiation is illustrated in Fig 1 With the patient placed in a suitable position, the anatomical outlines of two body sections are traced with the aid of dental moulds An individual perspex jig is prepared from these so that it is possible to bring the patient into the correct position at every treatment and also to secure accurate positioning of the beam nozzle

A roentgenogram of the treatment area, with the flexible magnification indicator applied to the patient s skin and produced in the treatment position prescribed, is shown in Fig 2 This film is used for determination of the distance from the skin to the anterior and posterior borders of the larynx and to the spinal cord

Table

Five year results of treatment of carcinoma of the larynx at Radiumhemmet during 1953—1958

Category	Patients treated	Deaths free of cancer	Determinate cases	Symptom free	Corrected cure rate
Supraglottic					
T I	3	—	3	2	2/3
T II	1	—	1	—	0 1
T III	4	1	3	2	2/3
T IV	9	—	9	3	3/9
Total	17	1	16	7	7/16 (44)
Glottic					
T I	60	11	49	45	45/49
T II	24	5	19	13	13/19
T III	21	4	17	14	14/17
T IV	1	—	1	—	0 1
Total	106	20	86	72	72 86 (84 %)
Total material					
T I	63	11	52	47	47/52
T II	25	5	20	13	13/20
T III	25	5	20	16	16 20
T IV	10	—	10	3	3/10
Grand total	123	21	102	79	79/102 (77 %)

symptom free after 5 years because of surgery have been counted as not symptom free after 5 years Patients who died within 6 months have been counted as dead from cancer

The glottic carcinomas represent the largest group as there were no primary subglottic and only few supraglottic tumours in the material

The above mentioned 1963 recommendations on clinical stage classification of malignant tumours of the larynx given by the International Union Against Cancer define only the different T N and M categories No proposition is made as to their combination into stages as did the corresponding 1958 recommendations We have therefore used the T categories alone for the classification of the present material and feel that this mode of classification offers better possibilities of drawing conclusions as to the suitability of a certain treatment method for tumours differing in position and size We further believe that it would be of value if the classification in T-categories took the mobility of the cords into

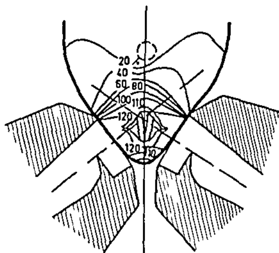


Fig 3 Dose distribution with a two field short distance cobalt technique with special wedge filters

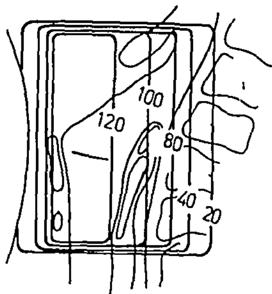


Fig 4 Dose distribution in the sagittal section with a 6 cm high field

fully controlled It is wise in general to chose a field height of 6 cm in order to avoid subglottic recurrences If larger tumour dimensions, more deep growth, or regional metastases are present or suspected it is advisable, when radiotherapy is chosen, always to use the kilocurie cobalt treatment techniques

The present material dates from the year 1953 when detailed individual treatment plannings and dose calculations in carcinoma of the larynx began to be performed It consists of 123 patients treated in the years 1953 to 1958 114 being men (93 %) and 9 being women (7 %) Only primary cases with a histologically proven, infiltrating squamous cell carcinoma have been included No patients have been lost to follow up The material has been classified according to the T categories, proposed for malignant tumours of the larynx by the Committee on Clinical Stage Classification and Applied Statistics of the International Union Against Cancer in 1963 It may be mentioned that group T—I consists of tumours confined to one anatomical site within the larynx, T—II of tumours confined to one anatomical region within the larynx, T—III of tumours extending beyond one anatomical region but confined to the larynx, and T—IV, lastly, of tumours extending beyond the larynx

The 5 year results by irradiation alone, giving the rates of cure are presented in the Table below Thus, patients with recurrence after irradiation, who were

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consideration, as was the case in the 1956 recommendations The glottic T—II group ought especially to be divided into patients with full mobility retained and patients with mobility impaired or lost, since such sub groups have a very different prognosis We have not, however, employed any such sub division in the present case material, since the number of patients treated was considered too small On the other hand, the presence of patients with impaired or lost mobility of the vocal cords among the glottic T—II material apparently considerably influenced the corresponding cure rate

The 5 year cure rate for glottic carcinomas, corrected for intercurrent deaths, is 45/49 (92 %), 13/19 (68 %), and 14 17 (82 %) in groups T—I, T—II, and T—III, respectively (see table)

It appears that recurrences in patients without metastases seem to occur almost exclusively within the first three years This fact emphasizes the importance of frequent follow up examinations during the first years after treatment

SUMMARY

Teleradium units and from 1955 decacurie cobalt 60 units have been used for the treatment of laryngeal carcinomas The material consists of 123 cases of primary proven infiltrating squamous cell carcinoma supraglottic in 17 and glottic in 106 patients The 5 year irradiation cure rate for glottic carcinoma corrected for intercurrent deaths was 92 68 and 82 per cent in groups T I T II, and T III respectively

ZUSAMMENFASSUNG

Die Behandlung des Kehlkopfkarzinoms wurde mit Teleradium Bestrahlung und seit 1955 mit Decacurie Kobalt 60 Bestrahlung vorgenommen Im Ganzen handelte es sich um ein Material von 123 Fallen von primaren infiltrierenden Schuppenzellenkarzinom supraglottisch in 17 Fallen und intraglottisch in 106 Fallen Nach Korrektion fur dazwischen kommendes *Tod zeigten die Resultate eine 5jahrige Heilung in* 92 68 und 82 Prozent fur die Gruppen T I T II und T III

RÉSUMÉ

Des appareils de teleradiumtherapie et à partir de 1955 des appareils de cobalt therapie de 10—30 curie, ont ete utilises pour le traitement des cancers du larynx Le materiel des auteurs comprend 123 cas de carcinome epidermoide infiltrant verifie sus glottique dans 17 cas et glottique dans 106 cas Les taux de guerison de 5 ans corriges pour tenir compte des morts intercurrentes sont respectivement de 92 68 et 82 pour cent dans les groupes T I T II et T III

Effects of small radiation doses PAPE et coll described the beneficial effects of small doses of radiation and compared these to the cell destructive effects of high radiation doses The value of the small doses and the frequency of ir radiations are not important in relation to a protective mechanism Doses over 150 R are considered harmful The good effect of small radiation doses has in plants been found to consist of an improved tolerance to heat The beneficial effects are manifest in animals by a quicker healing of wounds (20) and bone fractures (32 44) as well as by improved resistance against toxins (3, 36) and resistance to tumour vaccinations (16) Since the protective effect of pre radiation with small doses is difficult to consider quantitatively PAPE chose for his investigations radiosensitive organs i e the spleen and testicle of the rat He observed a faster generation of the lymphoid tissue of the spleen and of the spermatogenic function of the testis when the tissue had been pre irradiated His work has b en confirmed by the studies of TRAUTMANN et coll The more recent studies of DIETHELM & LORENZ under the same conditions have not confirmed PAPE S work The reason for the contradiction in these results after radiation with small doses is not obvious DIETHELM believes the explanation to be that the cell populations studied were not homogenous i e the cells in the spleen and testes were in various stages of maturation and the radiation sensitivity may there fore have been dependent on the degree of maturity

Preradiation with large doses The influence of massive preradiation on the resistance of the organism has been studied in numerous experiments which have produced varying results Many media (yeast bacteria isolated cells in vitro small rodents mammals) and variable criteria have been used to study the preradiation effect on the resistance to infection (1 4 34 41 43), the rate of growth of transplanted tumor cells (1 17 18 39) improved tolerance to toxic drugs such as strychnine chlorethylene allyl alcohol (1 15) increased exercise tolerance (7), increased mitotic activity in duodenal crypt epithelium (6) and in haematopoieses

The effect of whole body irradiation with respect to increased resistance against the effects of a second exposure to radiation may be accurately measured by observation of the survival time In our opinion this is best expressed as the LD_{50} dose in relation to the time interval after exposure Some detailed references to changes in survival time in cases with prior exposure to large doses and a second radiation are cited below

RAPER stated that an antecedent non lethal dose of a whole body β irradiation of 3 000 rep in mice increased the LD_{50} from 4 700 rep to maximal 8 400 rep The interval between the first and second radiation exposure was 28 to 56 days The LD_{50} was found to be 6 700 rep from 3 days 7 600 rep from 7 days and 8 000 rep from 14 and 112 days respectively

FROM THE INSTITUTE OF RADIOLOGY OF THE FREE UNIVERSITY OF BERLIN,
WESTEND HOSPITAL, CHARLOTTENBURG, WESTERN GERMANY

ACQUIRED RADIORESISTANCE FOLLOWING WHOLE BODY IRRADIATION

by

V Taenzer and F Krokowski

In experimental studies in animals, a protective mechanism following whole body irradiation has been reported upon (1, 9, 10 11, 19, 21, 30, 31) This biologic protective mechanism has been found to be more effective and different from the well known recovery ability of the body after multiple irradiations and it will be discussed in the present paper

It appears from a study of the literature that two contradictory facts should be considered (1) a summation of the effects of multiple total body exposures to irradiation occurs, and (2) an adaptation of the organism similar to the experimentally proved acquired radioresistance in tumour treatment has also been observed (28, 35, 38) The present authors have in addition observed a protective mechanism that cannot be defined by these known conceptions of the response to irradiation A special analysis of published observations in the light of our own studies has enabled us, however, to present a single scheme capable of explaining the different experimental data

It is important to differentiate between small roentgen doses as used in the treatment of inflammatory conditions and radiation therapy in malignant conditions In surveying the literature on radiation sensitivity one must differentiate the responses obtained with small doses (up to 25 R) from those obtained with higher (sublethal to lethal) doses

Submitted for publication 18 April 1967

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In the studies of BETZ with mice, a single total exposure of 700 R was *found to* be lethal. If, however, the mice were first given 500 R, then the survival after a *second exposure to 700 R was found to be 20 % at 7 days, 26 %* at 10 days, 36 % at 15 days, and 0 % at 33 days.

KISELEV, in similar experiments with mice, found that the LD_{90} from a single exposure to radiation was 700 R. The effect of pre-irradiation with 110 R given once, twice or three times, at an interval of one week followed in two weeks by a second exposure to 700 R, resulted in survivals of 75 %, 50 %, and 17.5 %, respectively.

In a communication by DAQUISTO, the $LD_{50(30)}$ of white mice increased from 487 to 560 R after preradiation with a dose of 50 R ten days before, and from 487 to 617 R when the preradiation was given 17 days before.

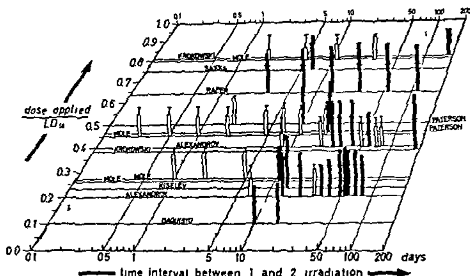
PATTERSON et coll. gave mice half of the LD_{50} dose and determined the new LD_{50} *dose after different time intervals with increasing doses of whole body irradiation.* During a time interval of two days, the LD_{50} was reduced from 518 to 493 R. *With a longer interval from 10 to 20 days* between the first and second irradiation, the new LD_{50} was increased from 728 to 799 R. In a similar study in the rhesus monkey (30), it was shown that 20 days whole body irradiation with 200 R the LD_{50} increased from 570 to 623 R.

SAKKA & KAMATA irradiated a group of mice with 1/2 LD_{50} (= 350 R) which a week later gave a LD_{50} of 480 R. Only 37 % of the animals died. A second group of animals, under equal conditions, were given 1/2 LD_{50} with the sieve method, and in these animals the mortality was only 33.5 %. The result seems to underline the advantages of the sieve method.

Analogous observations of a diminished mortality rate due to pre-irradiation were reported by DIMITROW, and by GRAEVSKAJA & KEJLINA in experiments in dogs.

BRAUN, and numerous other authors (6, 20, 22) were on the other hand *unable to confirm that pre-irradiation* had any beneficial effect on survival following a second dose of radiation. Rats, which were irradiated with doses of *200, 350,* and *500 R, during time intervals of 4, 6, and 10 days before* a lethal dose, died earlier than controls that were irradiated only with the lethal dose.

We have in our experiments *found a significantly decreased effectiveness of* a second exposure to radiation in rats earlier irradiated with large doses. A preradiation of 750 R with the sieve method raised the $LD_{50(30)}$ following the second exposure to radiation without a sieve, from 925 R to 1 850 R after a time interval of half a year. In another study, we also gave the second radiation exposure dose with a sieve: the $LD_{50(30)}$ was then raised from 1 950 R to 3 000 R. Detailed information about these experiments has been published earlier (40).



Dose/Time effect relations for the LD_{50} after preradiation. The columns characterize the biologic effect (LD) of a second irradiation.

White columns: $\frac{\text{radiation effect with preradiation}}{\text{radiation effect without preradiation}} < 1$

Black columns: $\frac{\text{radiation effect with preradiation}}{\text{radiation effect without preradiation}} > 1$

The white ground area represents the limits of the observations of raised radioresistance.

Discussion

Limitations of increased radioresistance. The investigation of recovery after irradiation led to the discovery of the ability of radiation to increase the radioresistance. To explore the different degrees of recovery after irradiation depending on the time intervals, the LD_{50} was determined at different time intervals after one or more exposures to radiation. It is surprising to encounter the so-called effect of over-compensation of the recovery after a period of complete recovery. DAQUISTO suggested that the size of the dose at the primary irradiation as well as the length of the time interval between the first and second irradiation are important factors in relation to an increased radioresistance.

It would appear that all the confusing observations from a summation of effects to no effects at all or to a decrease in the effects caused by the radiation can be summed up in one hypothesis unifying all the known observations. The cause of the contradictions was thought to lie in the dose/time correlations which frequently are not sufficiently taken into consideration.

The influence of the time interval between two irradiations upon the increase in radiation sensitivity can be comparatively easily recognized Time intervals of irradiation from several hours to a few days lead to a summation of the radiation hazards Prolongation of the time interval between irradiations leads after an indifferent phase to a decrease in the radiation sensitivity for long time intervals (> 10 days)

The size of the dose of preradiation is equally important The observations reported in the literature vary with the age, sex and race of the animals irradiated, as well as with the quality of the radiation used, and on the evaluation of the effect observed The recovery periods are reported to be faster in primates than in rodents, faster in mice and rats than in guinea pigs, and to be especially slow in amphibians (30) An additional difficulty lies in the sometimes reported fractionation of the preradiation

In our analysis of the dose/time/effect relations we only took account of those observations in the literature in which the preradiation had been given in a single dose and in which the biologic effect was clearly measurable Race, age and sex could be neglected since only the LD_{50} was evaluated, which is characteristic for each race and genotype

In summarizing the observations all the doses applied were considered as fractions of the characteristic LD_{50} from each race This LD_{50} was used, and it was compared to the LD_{50} of observations without any preradiation, i e

$$\frac{\text{radiation effect } (LD_{50}) \text{ with preradiation}}{\text{radiation effect } (LD_{50}) \text{ without preradiation}}$$

A value less than one in this scheme means that because of a partial summation of radiation effects the LD_{50} is decreased after a second irradiation Values above one indicate the protection effect of a second radiation dose in pre irradiated animals If the results are standardized in the way described above and put in a three dimensional coordinate system in which the ground area represents the dose applied (fraction of the LD_{50}) and the time interval between the first and second irradiation, and in which the length of the columns expresses the effectiveness of a second radiation, a dose time/effect scheme is obtained (see the accompanying figure) In considering this scheme it is feasible to outline the limits in which the protective mechanism after a second radiation becomes effective

Influence of the time interval During the first days following radiation the radiation sensitivity is diminished With prolongation of the time interval between the first and second irradiations the organism recovers and the endurance of

radiation enhances slowly Around the 8th to 10th day a period with clearly improved radioresistance is then recognizable and lasts at least 200 days

Influence of the size of the preradiation dose Small doses of primary radiation (below 5 % of the LD_{50}) release no protective effect This effect becomes obvious when the primary radiation dose is higher than 10 % of the LD_{50} In cases in which the preradiation exceeds 80 % of the LD_{50} the protective mechanism does not develop

This dose/time/effect scheme indicates that the varying observations in the literature may be evaluated from one standpoint An enhanced radioresistance will not occur if the time interval between the first and second radiation doses is too short or if the dose of the primary radiation is too high or too low

Mechanism leading to improved radioresistance Each dose of radiation results in an unspecific stimulation of the organism The reaction of the organism is determined by the hypophyseal adrenal system and promotes an increase in dynamics The favorable effect of small radiation doses may be understood by the adaptation of the organism in this sense Large doses of radiation overcome the effect which becomes unimportant since cell destruction promotes different ways of reaction of the organism i e denaturation of protein which leads to an antigen antibody reaction and to the development of complement binding antibodies Changes in the immunologic pattern of the organism after irradiation were suggested by the observation that the blood of irradiated animals releases a protective effect against radiation in other animals in which transfusion has taken place

Furthermore characteristic changes in serum protein electrophoresis have been reported with an augmentation of antibody transferring gamma globulin at 10 days after irradiation i e at the beginning of the phase of raised radioresistance KISELEV et coll (1956) succeeded in directly demonstrating the complement binding antibody The antibodies are demonstrable for three to four months which is about the length of time of the increased radioresistance The titres of the antibodies and the radioresistance follow an almost parallel decline Multiple pre irradiations and too high single radiation doses damage the antibody producing RES and the antibody building ability is thus diminished in spite of large protein denaturization On the other hand doses that are too small do not allow protein denaturization and antibody production

Further experiments will be needed for a better understanding of the mechanisms of protection development after irradiation which are still known only to a small extent

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Further experiments will be needed for a better understanding of the mechanisms of protection development after irradiation, which are still known only to a small extent

Acknowledgement

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SUMMARY

The investigation has demonstrated that each whole body irradiation of animals influences the dose/effect relation of a second irradiation The data indicate that a protective mechanism correlates to the primary dose applied and to the *time interval* Only under special circumstances did whole body irradiation promote protection against a second irradiation

ZUSAMMENFASSUNG

Jede Ganzkorperbestrahlung beeinflusst die Beziehung Dosis/Effekt einer folgenden zweiten Bestrahlung *Die Analyse tierexperimenteller Ergebnisse* zeigt dass die *Ausbildung* eines Schutzmechanismus von der Hohe der Vorbestrahlungsdosis und dem Zeitintervall zwischen beiden Strahlenexpositionen abhangt Nur unter bestimmten Voraussetzungen kann eine Ganzkorperbestrahlung vor einer zweiten Bestrahlung schutzen

RÉSUMÉ

Cette expérimentation montre que chaque irradiation de tout le corps d animaux influe sur le rapport dose/effet d une seconde irradiation Les resultats des experiences montrent que le mecanisme protecteur est lie à la premiere dose appliquee et à l intervalle de temps C est seulement dans des circonstances speciales que l irradiation de tout le corps confere *une protection contre une seconde irradiation*

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FROM LABORATORIO DE ISOTOPOS ABÍLIO LOPES DO REGO AND THE TELEGAMMA THERAPY UNIT, INSTITUTO PORTUGUES DE ONCOLOGIA FRANCISCO GENTIL, AND CENTRO DE ESTUDOS DE MEDICINA NUCLEAR INSTITUTO DE ALTA CULTURA LISBOA PORTUGAL

RENOGRAPHIC ANALYSES IN RADIATION THERAPY OF CARCINOMA OF THE UTERUS

by

M BRITES PATRICIO and A M BAPTISTA

An examination with radioisotopes is a simple and practical means of separately determining the function of the kidneys The method was first proposed in 1956 for the study of renal disease and hypertension and consists of the intravenous introduction of a radioactive material with selective renal excretion NORDYKE (1960) utilized hippuran labelled with ^{131}I for the first time and proved its superiority to substances previously employed RODDICK GERBIE & FLANAGAN (1964) studied urinary tract disfunction associated with gynecologic operations DISCHE (1963) on isotope examination of cervical carcinoma cases found that 50 % of 90 cases studied more than three months after treatment were abnormal and 30 % of 17 new cases had delayed drainage RODDICK et coll reported the results of an investigation of 26 gynecologic cases all of which were subjected to radiotherapy MELDOLESI et coll (1964) published the results of an isotope examination in 21 cases of carcinoma of the uterus and reported an incidence of urinary tract complications in 57 % of the

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Table 1

Results of isotope examinations before irradiation in 141 cases of carcinoma of the uterus

Stage	Number of cases	Per cent of cases	Normal findings		Abnormal findings				
			No	%	Unilateral alteration			Bilateral alteration	
					Right	Left	%	No	%
II	29	20.5	15	51.7	3	3	20.8	8	27.5
III	61	63.3	10	16.4	12	1	21.3	38	62.3
IV	17	12.1	3	17.6	—	3	17.6	11	64.8
Postoperative	34	24.1	20	58.8	2	1	8.8	11	32.4
Total	141	100	48	34.2	17	8	17.5	68	48.3

cases DEWULF et coll (1964) were of the opinion that this test was more sensitive than urography and gave indications of stasis when urography still gave strictly normal findings

All of these authors pointed out the great advantages of the radioisotope function test for the study of the urologic conditions in gynecologic cases, because of its sensitivity, high tolerance, great simplicity and easy reproducibility

The study of 141 cases of carcinoma of the uterus, in which the present authors have carried out 257 isotope examinations before and after gamma radiation therapy, are presented in this communication

Material and Method All patients fast for 12 hours prior to the study The kidneys are localized with an intravenous injection of chloromerodrin labelled with ^{203}Hg (1 μCi) (Radiochemical Center, Amersham, England) administered 20 minutes before beginning the examination The posterior surface of each kidney is identified by careful positioning of a large angle collimated scintillation probe until the points of maximal radioactivity are observed, with patient in prone position Thereafter 0.5 μCi per kg bodyweight of sodium iodohippurate, labelled with ^{131}I, according to the technique used by MITTA FRAGA & VEALL (1961) and by CEIA, LIMA & BAPTISTA (1965) are injected into an antecubital vein The radioactivity, as detected by the scintillation detector, is registered with a recorder coupled to a ratemeter

A prolonged uninterrupted accumulation of the radionuclide occurs whenever there are alterations in the outflow of the urinary tract, as often happens in advanced stages of carcinoma of the cervix This is reflected by a

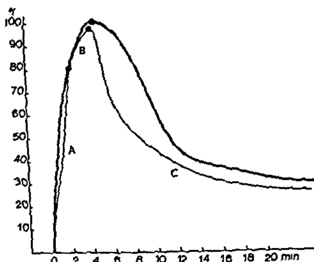


Fig 1 Bilaterally normal isotope examination in a case of carcinoma of the cervix stage II Labelling of curve components A — initial spike B — accumulation phase (secretion of functional segment) C — excretory phase

continuously rising tracing if related with eventual complete obstruction of the urinary tract The excretory phase is very slow when there is incomplete obstruction Considerably prolonged complete or incomplete obstruction leads to a secondary alteration of the renal parenchyma indicating hypofunctioning or absence of kidney and the renogram is characterized by a low level vascular peak which is followed by a plateau We obtained 257 renograms in our 141 cases of carcinoma of the uterus The cases were divided into four groups

1 Carcinoma of the cervix stage II	29 cases
2 Carcinoma of the cervix stage III	61 cases
3 Carcinoma of the cervix stage IV	17 cases
4 Adenocarcinoma of the corpus uteri operated upon	34 cases

Renograms were obtained prior to gamma therapy in all the cases and in 74 cases the examination was repeated after treatment in some cases more than once

The patients were treated by cobalt teletherapy or cesium teletherapy with the technique of four fixed fields or with a pendular technique The tumour dose varied from 4 000 rad to 7 000 rad administered during four to seven weeks In some cases the external radiation was followed by curie therapy so

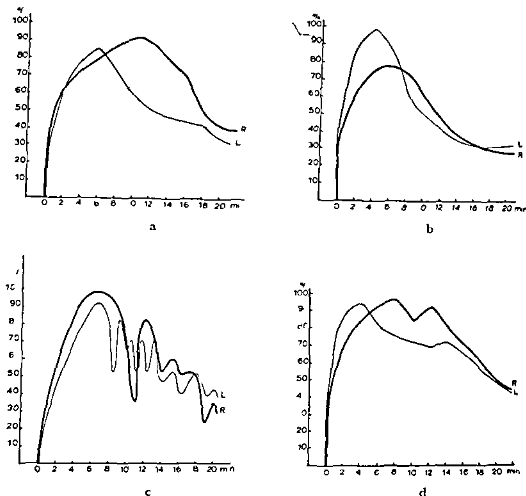


Fig 2 Case 1 Isotope examinations a) Renogram before gamma therapy Incomplete obstruction on the right side b) About 2 months later in the middle of the treatment period Total recovery c) Renogram obtained immediately after curie therapy Intermittent outflow oscillations d) Ten days after radiotherapy Marked bilateral obstruction

that the combination of radium and telegamma therapy was calculated to deliver approximately 8 000 rad to point A and just less than 5 000 rad to point B These points are the ones usually considered in curie therapy

Results

A greater frequency of invasion of the left parametrium was observed in 107 cases of carcinoma of the cervix

The results of the renographic examinations before radiotherapy are given in Table 1 Of the 29 cases in stage II, 51 7 % were of normal appearance,

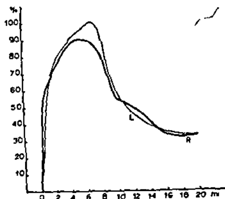
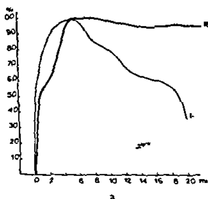
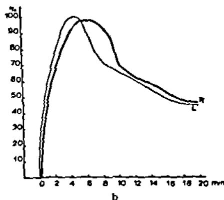


Fig 3 Case 1 Renogram obtained six months after treatment The appearances are normal





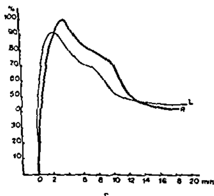


Fig 4 Case 2 Isotope examinations a) Renogram obtained before irradiation Total obstruction on the right and partial obstruction on the left side b) After cesium teletherapy Total recovery c) Three months after treatment Normal appearances

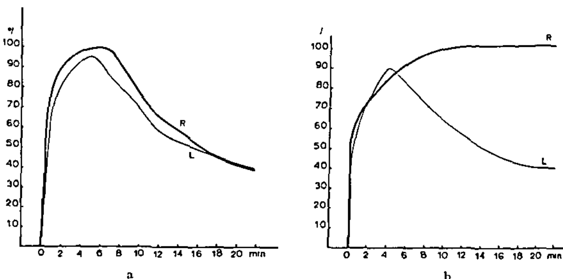


Fig 5 Case 2 Isotope examinations a) Six months after treatment Normal appearances b) Last test performed nine months after treatment revealed marked obstruction on the right side (The gynecologic examination disclosed recurrence)

20 8 % had unilateral alterations, and 27 5 % had bilateral alterations Of the 61 cases in stage III, 16 4 % were of normal appearance, 21 3 % had unilateral and 62 3 % bilateral alterations Of the 17 cases in stage IV, 17 6 % had normal signs, 17 6 % had unilateral and 64 8 % bilateral alterations Of the 34 cases operated upon, 58 8 % had no changes, 8 8 % had unilateral and 32 4 % bilateral alterations

It is evident that the right kidney is the more frequently disturbed in cases with unilateral alterations Considering all the cases, 93 (66 %) had abnormal, and 48 (34 %) normal renograms (Fig 1) Repeat examination after radiotherapy was performed in 74 cases, a few of which are presented below

Case reports

Case 1 Stage II This was abnormal before gamma therapy (incomplete obstruction on the right side) Examination in the middle of the treatment indicated recovery Outflow oscillations in relation to marked peristaltic waves were observed immediately after curie therapy Ten days after radiotherapy a further test disclosed marked bilateral obstruction (Fig 2) Six months later the test (Fig 3) and the gynecologic examination were negative

Case 2 Stage IV On examination before irradiation total obstruction on the right and partial obstruction on the left side were demonstrated (Fig 4a) A further test immediately after cesium teletherapy indicated total recovery (Fig 4b) Examinations performed three (Fig 4c) and six months later (Fig 5a) showed normal conditions The last test performed nine months later (Fig 5b) revealed marked obstruction on the right side and the gynecologic examination suggested recurrence

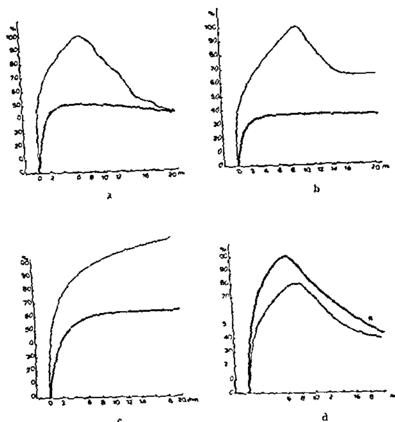


Fig 6 Case 3 Isotope examinations a) Before treatment Outflow obstruction and diminution of function of right kidney b) Immediately after radiotherapy and (c) about a month after radiotherapy Abnormal appearances d) One year later Normal sign

Case 3 Stage III Diminution of function on the right side Two tests performed after radiotherapy both revealed deterioration One year later the appearances were normal and the patient was well Cytologic investigation was negative (Fig 6)

A summary of the results of repeat examination, before and after irradiation in the 74 cases is presented in Table 2 In 12 2 % of these the appearances returned to normal in 22 9 % partial recovery took place and in 4 1 % slight recovery was noted There was no improvement in 24 3 % deterioration in 14 9 % and 21 6 % remained normal

A correlation is presented in Table 3 between the clinical course and the finding in isotope examinations in 61 cases of carcinoma of the cervix

Table 2

Summary of results in 74 cases with repeat examination before and after irradiation

		Stage II		Stage III		Stage IV		Post operative		Total	
		No	%	No	%	No	%	No	%	No	%
Recovery	*Total*	4	21 1	3	9 1	—	—	2	15 4	9	12 2
	Partial	3	15 8	11	33 3	2	22 2	1	7 7	17	22 9
	Slight	—	—	2	6	1	11 1	—	—	3	4 1
Without improvement		6 N 3 P	47 4	6 N 8 I	18 2 24 3	1 N 4 P	11 1 N 44 5 P	3 N 3 P	46 1	16 N 18 P	21 6 N 24 3 P
Deterioration		3	25 7	3	9 1	1	11 1	2 N 2 I	30 8	11	14 9
	Total	19	25 7	33	44 6	9	12 2	13	17 5	74	100

Discussion

The results indicate the high frequency of urologic complications in carcinoma of the uterus We could not say, however, to what extent the inflammatory alterations of the parametrium were responsible for the complications The examination with hippuran ¹³¹I is an effective method of demonstrating urinary tract abnormalities resulting from gynecologic disturbances, it is simple to perform, is well tolerated by the patient, and in practice presents no contra indications Its use would therefore appear justified in all cases of carcinoma of the uterus

Abnormal appearances do not necessarily indicate the site of an obstruction, however, and it is often advisable to follow up with urography The isotope examination is not meant to replace urography but to supplement it It certainly constitutes an alternative in the long term follow up of cases of carcinoma of the uterus, since it is readily available, is better tolerated costs less and is a highly sensitive test

It appears that a normal isotope examination is of good prognostic value All cases except one in stage II were well and without recurrence one year after treatment Of the six cases in stage III, five were well and without recurrence, and only one case was without improvement 14 months later One case in stage IV was well one year later

The results also demonstrate that the isotope examination is valuable It supplements the findings of the clinical examination with respect to invasion

Table 3

Renographic findings in relation to the clinical progress

	Stag	Number of cases	Alive		Dead	Lost	Months of observation		
			With lesions	Without lesions			0—6	6—12	12—24
Normal appearances before irradiation (21)	II	6	1	4	—	1	3	1	[illegible]
	III	6	1	5	—	—	2	2	2
	IV	1	—	1	—	—	—	—	1
Total recovery (11)	II	4	1	3	—	—	2	1	1
	III	3	1	2	—	—	—	—	3
	IV	—	—	—	—	—	—	—	—
Partially improved (31)	II	3	1	1	—	1	2	1	—
	III	13	3	4	—	6	10	2	1
	IV	3	2	1	—	—	3	—	—
Abnormal appearances without improvement after irradiation (25)	II	3	1	—	—	[illegible]	2	1	—
	III	8	2	2	1	3	5	2	1
	IV	4	2	—	—	2	3	—	1
Deterioration after irradiation (7)	II	1	1	—	—	—	—	—	1
	III	2	2	—	—	—	—	—	2
	IV	1	1	—	—	—	1	—	—
Normal appearances before irradiation and abnormal after irradiation (3)	II	2	1	—	—	1	1	—	1
	III	1	—	—	—	1	1	—	—
	IV	—		—	—	—	—	—	—

of the parametrium and allows an evaluation of the irradiation effect in gynecologic cases

We could not ascertain to what extent the deterioration indicated by the renogram may have been due to oedema One case with an abnormal isotope examination immediately after the treatment showed no abnormal features two months later In another case total recovery was recorded in the middle of the treatment period while at its termination the examination disclosed bilateral obstruction Six months later the appearances were again normal

Continuation of the abnormal appearances at the isotope examinations is a bad prognostic sign although it would seem as if ureteral stasis may exist without any indication of recurrent or persistent disease This was observed

in a woman with carcinoma of the cervix, stage III, in whom the follow up examinations after gamma therapy indicated deterioration This patient was well, though clinically induration of the parametrium was observed The histologic analysis was negative The signs of deterioration must be attributed exclusively to irradiation fibrosis

We feel that it is of great value to perform isotope examinations not only during the follow up cases of carcinoma of the uterus treated with ionising radiation but also in all gynecologic cases before beginning any treatment, this because of the prognostic importance related to the knowledge of any eventual abnormality of the urinary tract

SUMMARY

In 141 cases of carcinoma of the uterus 257 isotope examinations of the kidneys with hippuran ^{131}I were performed before and/or after radiotherapy The results revealed that these tests are useful for demonstrating invasion of the parametrium and allow objective evaluation of the therapeutic effect of irradiation in gynecologic cases

ZUSAMMENFASSUNG

An 141 Fallen von Uteruskarzinom wurden 257 Isotopen Untersuchungen der Nieren funktion mit Hippuran ^{131}I bevor und/oder nach Strahlentherapie vorgenommen Die Resultate zeigten dass solche Untersuchungen sehr wertvoll sind um eine Invasion des Parametriums zu entdecken und um den Erfolg der Strahlentherapie zu beurteilen

RÉSUMÉ

Les auteurs ont fait deux cinquante sept examens isotopiques des reins avec l hippuran ^{131}I dans 141 cas de cancer de l utérus ou il y avait une indication clinique de radiothérapie Les résultats ont montré que ces examens sont utiles pour mettre en évidence l invasion du parametrium et pour permettre de juger objectivement l effet thérapeutique de l irradiation dans les affections gynécologiques

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FROM THE DEPARTMENT OF RADIATION BIOLOGY AND BIOPHYSICS, UNIVERSITY OF ROCHESTER, NEW YORK, U.S.A., AND THE SPECIAL LABORATORIES OF STATENS STRÅLSKYDDSINSTITUT, STOCKHOLM, SWEDEN

ABSORPTION OF ^{212}Pb FROM THE GASTROINTESTINAL TRACT OF MAN

by

JOHN B. HURSH and JORMA SUOMELA

For the calculation of radiation hazard from ingestion of lead isotopes it is necessary to specify the fractional amount which is absorbed from the gastrointestinal tract. The ICRP 1959 Report lists a value of 8 per cent based on experiments with stable lead. Because of the possibility that carrier free lead of high specific radioactivity might behave differently, ^{212}Pb, the 10.6 hour half life daughter of thoron, was administered to four volunteer subjects. Subject A received one oral and one intravenous dose, subjects B and C each received a single oral dose, and subject D received a single intravenous dose. Based on the fractional amount excreted in the urine after intravenous injection it was estimated that absorptions of 1.3, 8.1, and 16 per cent had occurred when ^{212}Pb was taken by mouth.

Preparation of dose. The ^{212}Pb dose for oral consumption was prepared by passing a stream of 50 per cent O_2 – 50 % CO_2 through a 0.7 mCi, Th

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stearate, filter cartridge source (HURSH & LOVAAS) sweeping the released thoron gas through a fritted glass bubbler stuck into 250 ml of beer at a gas flow rate of 50 ml per min The beer was contained in a 2 liter glass bottle Recovery of ^{1}Pb using beer as the vehicle was superior to recovery using coca cola weak ascorbic acid solution or physiologic saline It was assumed that the foam generated by the bubbling process tended to hold the 55 6 s half life thoron captive until decay occurred Although the end product was somewhat flat the subjects found it palatable The period of thoron flow was adjusted so as to provide a ^{1}Pb activity equal to about 5μCi at the time of ingestion A delay of > 10 hours was introduced between preparation and ingestion to ensure transient equilibrium between ^{1}Pb and its 60 5 min half life ^{1}Bi daugther

A similar method was used to prepare the intravenous dose except that 20 ml of physiologic saline in a 1 liter plastic bottle was used as the vehicle Subsequently the saline solution containing ^{1}Pb was transferred to a silicone coated penicillin bottle for sterilization prior to the injection of 10 ml (about 1 μCi ^{1}Pb) into the antecubital vein

In all cases gamma measurement of the preparation bottles plastic syringes or drinking vessels and transfer vessels showed that delivery of dose was better than 99 per cent complete Aliquots of the dose were routinely set aside for later verification

Doses were administered 1 to 2 hours after a light breakfast

Sample collection and measurement The subjects saved all urine and feces voided until the radioactive content decreased below the sensitivity of the counting method Collection was made directly into 1 liter plastic cartons The samples were measured for gamma activity by placing the collection carton on the upper surface of a 10 cm diameter 10 cm thick NaI(Tl) crystal detector surrounded by a shielded compartment The phototube output was fed into the first quarter of a 512 channel spectrum analyzer calibrated to 16 keV per channel The ^{1}Pb band was taken from 0 to 0 4 MeV and the ^{1}Bi band from 0 416 to 2 00 MeV Calibration constants were established by measuring freshly prepared standardized ^{1}Pb solutions at intervals during the growth of ^{1}Bi and by including a solution volume range equivalent to that of the samples These data enabled calculation of the correction factor to be applied to the counts in the ^{12}Pb band to take account of the Compton contribution from the ^{1}Bi gammas For example given a urine sample of 200 ml the conversion constant for ^{1}Pb was 195 cpm per nCi and for ^{1}Bi was 130 cpm per nCi The Compton correction was 0 87 times the cpm in the ^{1}Bi band Backgrounds were about 350 cpm for the ^{21}Pb band and 215 cpm for the ^{1}Bi band Counting times were 20 to 40 min per sample Sample volumes were estimated by weighing

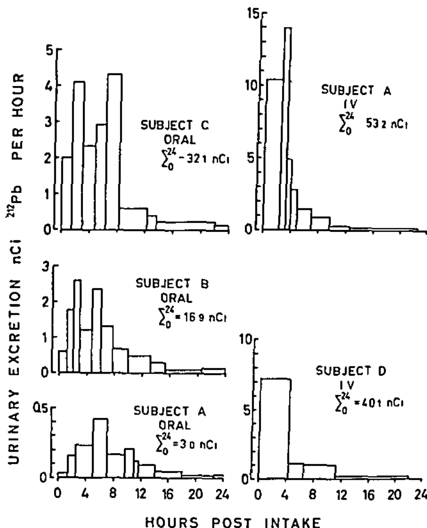


Fig 1 ^{212}Pb urinary excretion rate as a function of time for oral and intravenous intake

Twenty milliliters blood samples were taken from the antecubital vein using heparin as anticoagulant, and sampling at the times noted in the report of the results The blood was centrifuged within 3 min after collection and the plasma was separated from the cells Each fraction was weighed and counted for gamma radioactivity A 5 cm diameter, 5 cm thick NaI(Tl) crystal was used as detector and two measurements were taken for each sample using single channel analyzer settings such that the ^{212}Pb and ^{212}Bi activity could be estimated separately The blood fractions were next digested with conc HNO_3 and hydrogen peroxide The ^{212}Pb without addition of carrier was separated by use of the dithizone method (GIBSON) The 10 ml weak nitric acid solution containing

Table I

Absorption of orally administered ^{212}Pb calculated by comparing the urinary excretion with that after intravenous administration

Subject	Age yr	Wgt kg	Dose µCi	Mode	Urinary loss* nCi/24 hours	Absorption µCi	Absorption % dose
A	59	75	1 08	iv	53 2	—	—
D	39	76	1 17	iv	40 1	—	—
A	59	75	5 05	oral	2 98	0 067	1 3
B	40	84	5 01	oral	16 9	0 404	8 1
C	27	63	4 80	oral	32 1	0 768	16 0

* Activity decay corrected to midpoint of collection interval

the separated ^{212}Pb was evaporated on a 5 cm diameter stainless steel planchet yielding an essentially weight free deposit After a lapse of 6 hours or more to permit ^{212}Pb—^{212}Bi equilibrium to occur the planchet was counted for alpha activity in close proximity to a zinc sulfide layer phototube detector The overall counting efficiency was 34 per cent as determined by comparison with a RaD + E standard Chemical recovery was estimated by performing 10 analyses in which known amounts of ^{212}Pb were added to red cell and plasma samples from non radioactive donors The results indicated an average recovery of 90 per cent with a standard deviation of ± 7 per cent This correction was applied to the experimental data

Whole body counting At intervals the subjects were counted in the low back ground laboratory (LINDELL & MAGI) at this institute The procedure included scanning measurements and a series of localization studies For both purposes the subject lay in a supine position The arrangement for scanning used three 12 7 × 10 2 cm NaI(Tl) crystals placed equidistant on a collar surrounding the subject with each crystal face 40 cm from the subject s longitudinal axis During measurement the collar has a reciprocating motion as well as a movement parallel to the subject axis Details are available in the Whole Body Counter Directory of IAEA For localization studies a single crystal looked through a 5 cm wide aperture formed by two 1 cm thick lead plates The counting rate of a point source (^{212}Pb) moved along the longitudinal axis of the subject position decreased by half when removed in either direction from a point directly under the crystal center to a point 10 cm distant In the experimental procedure each position was counted from the dorsal and the ventral aspect of the subject The

counts obtained were stored in a 400 channel spectrum analyzer, read out, and converted to activity according to techniques in general use.

Conversion to absolute activity units. The basis for estimating absolute activity depended on direct or indirect alpha counting rate comparison with a U.S. Bureau of Standards RaD + E standard. Secondary standards prepared by passing thoron through 0.5 N HNO_3 solutions were calibrated by evaporating aliquots on stainless steel planchets and by counting rate comparisons with the standard. The standardized solutions were useful for evaluating, by gamma counting rate comparison, the activity of substances such as beer and urine which leave residues when evaporated and were therefore not suitable for direct alpha counting.

Results

^{212}Pb in feces and urine. In the original planning of this research it was hoped that the personal habits of the subjects would conform to the ICRP gastro-intestinal model and that the oral dose would be completely cleaned from the gut by 31 hours as specified. In sober fact, by 31 hours after intake, subjects A, B, and C had cleared 23, 0, and 17 per cent of the oral dose, by 48 hours 82, 69, and 77 per cent, by 72 hours, 82, 69, and 77 per cent, and by 96 hours 99, 69, and 77 per cent. The above data are based on fecal sample measurements, with the measured activity decay adjusted to time of oral intake. The intervals without increase are periods in which no fecal samples were voided. As this pattern of excretion became apparent in the first oral experiment, it became evident that *gastrointestinal absorption of ^{212}Pb could not uniformly be determined by whole body counting techniques.* For example, if 10 per cent of a 5 μCi oral dose were absorbed, and if complete gut clearance required 96 hours, the absorbed ^{212}Pb would have decayed to 0.95 nCi, an activity below the threshold for measurement by this method. Accordingly, other methods were sought. The use of fecal measurements alone for a direct assessment of the unabsorbed ^{212}Pb was unsatisfactorily imprecise because of the large decay correction factor for low activity samples excreted at late times. Determination of absorption on the basis of the amount excreted in the urine in the first 24 hours was the method chosen. Accordingly, as stated above, the oral experiments were supplemented by two experiments in which ^{212}Pb was injected intravenously in order to define the per cent of the systemic burden which would appear in the urine.

The results of the measurements of urine samples from all five experiments appear in Fig. 1. Each sample was decay adjusted from the time of measurement to the mid point of the collection period. The cumulative excretion from

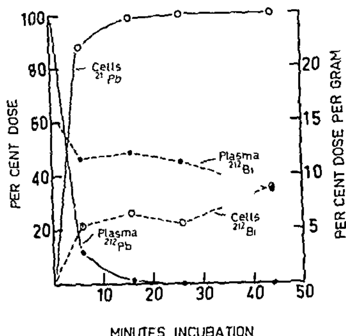


Fig 2 In vitro uptake of ^{212}Pb and ^{212}Bi by the blood cells The solid lines pertain to the left ordinate scale and the dotted lines to the right ordinate scale

0 to 24 hours was noted for each experiment By reference to the injected doses listed in Table 1 it may be calculated that when ¹Pb was administered intravenously 4 9 per cent (subject A) and 3 4 per cent (subject B) of the dose appeared in the 24 hour urine collection The average value 4 15 per cent was used to estimate absorption in the oral experiments yielding the results entered in Table 1

After intravenous injection subject A excreted 0 29 per cent dose in the fecal collection period 0 to 48 hours Subject D excreted 0 25 per cent dose for the same fecal collection period These estimates are maximized since all sample measurements were decay adjusted to injection time

¹Pb uptake by blood cells As an adjunct to the main experiments a preliminary in vitro experiment was performed in which 10 ml volumes of heparinized blood were incubated with added ¹Pb + ¹Bi at 37 C in a water bath At pre selected times the blood samples were removed and centrifuged The plasma and cell fractions were then assayed for ¹Pb and ¹Bi activity by gamma

Table 2

^{210}Pb and ^{210}Bi content of plasma and blood cells in per cent absorbed or injected dose per gram referred to sampling time except as otherwise indicated

Subject and mode	Sample	Hours post dose	Plasma ^{210}Pb*	Cells ^{210}Pb*	Cells ^{210}Pb**	Cells ^{210}Bi**	Cells ^{210}Pb t = 0	Total cells ^{210}Pb t = 0 % dose
A	1	0.33	0.00036	0.0106	0.0104	—	0.0107	32
intravenous	2	1.67	0.00009	0.0124	0.0140	—	0.0147	44
	3	4.05	—	—	0.0150	—	0.0195	59
	4	6.75	—	0.0124	0.0113	—	0.0184	56
	5	49.75	—	0.00054	—	—	0.0139	42
B	1	2.50	0.00009	0.0073	0.0057	0.0033	0.0077	26
oral	2	6.00	0.00009	0.0130	0.0116	0.0115	0.0182	62
	3	*8.00*	*0.00006*	*0.0136*	*0.0142*	*0.0111*	*0.0234*	*79*
	4	24.50	0.00006	0.0058	0.0031	0.0079	0.0221	75
C	1	2.60	0.00025	0.0086	0.0076	0.0052	0.0096	24
oral	2	6.10	0.00008	0.0124	0.0123	0.0096	0.0184	47
	3	8.00	0.00011	0.0132	0.0124	0.0117	0.0210	55
	4	24.50	—	0.0048	0.0055	0.0031	0.0255	65
	5	48.50	—	0.0010	0.0010	0.0012	0.0236	60
D	1	0.35	0.00033	0.0221	—	—	0.0226	69
intravenous	2	1.58	0.00011	0.0250	0.0260	0.0210	0.0285	89
	3	7.10	0.000052	0.0190	0.0200	0.0190	0.0310	93
	4	23.63	—	0.0059	0.0061	0.0060	0.0280	86
	5	47.57	—	0.0012	0.0016	—	0.0325	100

* Measured by alpha counting

** Measured by gamma counting

measurement as described above. The results are shown in Fig. 2. It is seen that at 16 min the cells have taken up 99 per cent of the ^{210}Pb added to the whole blood. The uptake of ^{210}Bi by the cells occurred at a slower rate and gives no evidence of a tendency to concentrate with respect to the plasma.

In view of these tendencies it is not surprising that the results after oral or intravenous administration as shown in Table 2 demonstrate only small amounts of ^{210}Pb in the plasma fraction of the drawn blood samples. The estimation of ^{210}Pb in the cells shows satisfactory agreement between the two measurement methods. The last column of the table lists results obtained by assuming that the total mass of circulating blood cells in grams is equal to 40.3 times the body weight in kg (BEST & TAYLOR). Since the ^{210}Pb content per gram cell (as shown

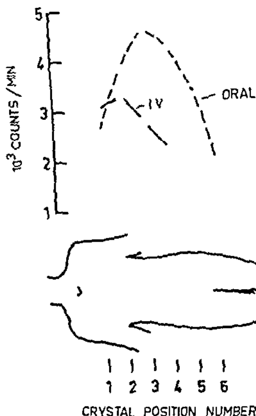


Fig 3 Comparison of radioactivity profile after intravenous (+6 hours) and oral (+ 28 hours) intake for subject A Actual counting rate was decay adjusted to time of intake and for oral results normalized to 1 μCi intake

in the next to last column) has been decay corrected to time of intake it may be seen that little if any ¹ Pb is lost except by decay The data for all subjects show an increase in cell content (last two columns) for the early sampling times believed to be due to the return of ²¹ Pb from the tissues to the blood as the plasma concentration is decreased leading to further uptake by the cell The generally higher estimates of ¹ Pb uptake in the total cells for subject D are obviously in error and it seems likely that the formula used to calculate the total cell mass resulted in an overestimate in this case It is recognized (GLASSER) that such formulae may be in error when applied to specific normal individuals

Comparison of ²¹¹Bi and ²¹¹Pb metabolism Although the data on the fate of ¹ Bi are less complete than are the data for ¹ Pb it has been found that at the time of voiding the bismuth activity in the urine samples is about twice that of

Table 2

^{212}Pb and ^{212}Bi content of plasma and blood cells in per cent absorbed or injected dose per gram referred to sampling time except as otherwise indicated

Subject and mode	Sample	Hours post dose	Plasma ^{212}Pb*	Cells ^{212}Pb*	Cells ^{212}Pb**	Cells ^{212}Bi**	Cells ^{212}Pb t = 0	Total cells ^{212}Pb t = 0 % dose
A	1	0.33	0.00036	0.0106	0.0104	—	0.0107	32
intravenous	2	1.67	0.00009	0.0124	0.0140	—	0.0147	44
	3	4.05	—	—	0.0150	—	0.0195	59
	4	6.75	—	0.0124	0.0113	—	0.0184	56
	5	49.75	—	0.00054	—	—	0.0139	49
B	1	2.50	0.00009	0.0073	0.0057	0.0033	0.0077	26
oral	2	6.00	0.00009	0.0130	0.0116	0.0115	0.0182	69
	3	8.00	0.00006	0.0136	0.0142	0.0111	0.0234	79
	4	24.50	0.00006	0.0058	0.0031	0.0079	0.0221	75
C	1	2.60	0.00025	0.0086	0.0076	0.0052	0.0096	24
oral	2	6.10	0.00008	0.0124	0.0123	0.0096	0.0184	47
	3	8.00	0.00011	0.0132	0.0124	0.0117	0.0216	55
	4	24.50	—	0.0048	0.0055	0.0031	0.0255	65
	5	18.50	—	0.0010	0.0010	0.0012	0.0236	60
D	1	0.35	0.00033	0.0221	—	—	0.0226	69
intravenous	2	1.58	0.00011	0.0250	0.0260	0.0210	0.0285	89
	3	7.10	0.000052	0.0190	0.0200	0.0190	0.0310	93
	4	23.63	—	0.0059	0.0061	0.0060	0.0280	86
	5	47.57	—	0.0012	0.0016	—	0.0325	100

* Measured by alpha counting
** Measured by gamma counting

measurement as described above The results are shown in Fig 2 It is seen that at 16 min the cells have taken up 99 per cent of the ^{212}Pb added to the whole blood The uptake of ^{212}Bi by the cells occurred at a slower rate and gives no evidence of a tendency to concentrate with respect to the plasma

In view of these tendencies, it is not surprising that the results after oral or intravenous administration as shown in Table 2 demonstrate only small amounts of ^{212}Pb in the plasma fraction of the drawn blood samples The estimation of ^{212}Pb in the cells shows satisfactory agreement between the two measurement methods The last column of the table lists results obtained by assuming that the total mass of circulating blood cells in grams is equal to 40.3 times the body weight in kg (Best & Taylor) Since the ^{212}Pb content per gram cell (as shown

Table 2. When the absolute concentrations of 210 Pb in the blood of subjects B and C are converted into per cent absorbed dose, the resulting values are quite comparable to those obtained in the two intravenous experiments. This would not be expected if the calculated systemic burdens of subjects B and C were greatly in error.

Proceeding on the grounds that the wide range in fraction absorbed is real, it is pertinent to inquire as to the possible causes of variation. The three subjects in the oral experiment were healthy active individuals. Compared with the ICRP (1959) reference man, who has 2 grams potassium per kg bodyweight, subjects A, B and C had 1.93, 1.89 and 2.63 grams per kg. These values suggest normal and above average ratios of lean body mass to total weight. The only suggestive relationship is the decrease in absorption of 210 Pb with increase in subject age. The present data are insufficient to prove age dependence and may represent fortuitous sampling of extremes on a curve of normal biologic variability. Either interpretation makes it likely that there is a group of individuals for which the absorption value of 8 per cent is not conservative for health protection uses. Further experiments are needed to define the size of this group.

Concentration of ²¹⁰*Pb in the blood cells.* The concentration of lead in the blood cells was observed by early workers (DAUWE 1907, BEHRENS et coll. 1927) and confirmed many times since. HEVESY & NYLIN (1953) reported that 6 hours after intravenous injection of 210 Pb into man 45 per cent of the injected amount was in the blood cells. STOVER (1959) found, for dogs, that 65 per cent of an intravenous dose of 210 Pb was in the blood cells at 5 hours. SCHUBERT & WHITE (1952) injected carrier free 210Pb into rats and detected 17 per cent of the dose in the blood cells at 30 minutes. The rate of loss from the red cells (not including radioactive decay) was 0.0187 per hour for dogs (STOVER) and 0.0231 per hour for rats (SCHUBERT & WHITE). HEVESY & NYLIN stated that in man the loss rate is less than 0.04 per hour.

The data in Table 2 show no consistant loss rate and render unlikely a loss rate greater than 0.007 per hour. If it be assumed for man that the death of the red cell releases the fixed lead and that the lead is removed from the body, for example by secretion in the bile, a minimum release rate can be calculated. Since the average life span of the human red cell is 120 days, the equivalent lead loss rate would be 0.0083 per day or 0.00035 per hour. Neither the data of HEVESY & NYLIN nor our findings can be regarded as excluding this interpretation. On the positive side a test of its feasibility can be applied by using data from the classical lead studies of KEHOE (1943). He found that the daily food intake of stable lead by occupationally unexposed individuals is about 0.35 mg and that the corresponding level in the blood is 0.030 mg per 100 ml. If the blood volume

the lead The blood cells in general show (Table 2) *slightly less* ^{212}*Bi than* ^{212}*Pb*, leading to the interpretation that the rate of ^{212}Bi loss from the cells must be low in respect to its rate of formation from ^{212}Pb HARBERS (1952) with ThX injected into rabbits, *found an excess of* ^{212}*Bi over* ^{212}Pb in the urine and the reverse to be true for the blood cells STOVER (1959), after intravenous injection of ^{212}Pb into dogs, found an excess of ^{212}Bi over ^{212}Pb in the urine, and no disequilibrium *for blood cells measured 20 min after sampling Finally, the whole* body counter localization studies in the present experiments showed no marked differences in the overall body distribution of ^{212}Pb and ^{212}Bi

Whole body counter findings Scanning measurements made with the whole body counter facility in the two intravenous experiments showed the expected 10 6 hour half life decrease *when small corrections were made for urinary* loss For the three oral experiments the activity found at the latest scan (about 48 hours), decay corrected to $t = 0$, yielded values of 18, 39, and 23 per cent of the *ingested dose for subjects A, B, and C As explained above, these amounts in*clude activity in the lower bowel which was voided subsequently With the exception of subject A, who voided 17 ± 1 per cent at 73 hours, the delay in voiding *resulted in activities near the threshold of detection, subject to large correction* factors for decay and not of use in the estimation of the absorbed fraction

The measurements with the lead columnated crystal yielded results of which *the data from examination of subject A presented in Fig 3 is a typical* example The oral experiment data, measured 28 hours after intake and normalized to time of intake and to 1 μCi dose, shows an activity peak in the lower bowel region The survey 6 hours after intravenous injection (counts corrected to injection time) shows a concentration of activity in the blood rich areas of the heart, lungs, and liver This result agrees well with what might be expected from the high ^{212}Pb content of the blood cells

Discussion

Absorption of ^{212}*Pb* The wide variation between the absorption of subject A and subject C (12 times) calls for comment The validity of the indirect method used to calculate absorption depends on the assumptions (1) that the fraction of the systemic ^{212}Pb excreted in the urine will be the same whether entry is via the gut or by intravenous injection and (2) that this fraction does not vary greatly from one healthy individual to another Both these assumptions are biologically plausible but proof that they apply to excretion of lead by man is lacking

Support for the calculated absorption values comes from the blood data in

Table 2. When the absolute concentrations of ^{212}Pb in the blood of subjects B and C are converted into per cent absorbed dose, the resulting values are quite comparable to those obtained in the two intravenous experiments. This would not be expected if the calculated systemic burdens of subjects B and C were greatly in error.

Proceeding on the grounds that the wide range in fraction absorbed is real, it is pertinent to inquire as to the possible causes of variation. The three subjects in the oral experiment were healthy active individuals. Compared with the ICRP (1959) reference man, who has 2 grams potassium per kg bodyweight, subjects A, B, and C had 1.93, 1.89, and 2.63 grams per kg. These values suggest normal and above average ratios of lean body mass to total weight. The only suggestive relationship is the decrease in absorption of ^{212}Pb with increase in subject age. The present data are insufficient to prove age dependence and may represent fortuitous sampling of extremes on a curve of normal biologic variability. Either interpretation makes it likely that there is a group of individuals for which the absorption value of 8 per cent is not conservative for health protection uses. Further experiments are needed to define the size of this group.

Concentration of ^{212}Pb in the blood cells. The concentration of lead in the blood cells was observed by early workers (DAUWE 1907, BEHRENS et coll. 1927) and confirmed many times since. HEVESY & NYLIN (1953) reported that 6 hours after intravenous injection of ^{212}Pb into man, 45 per cent of the injected amount was in the blood cells. STOVER (1959) found for dogs that 65 per cent of an intravenous dose of ^{212}Pb was in the blood cells at 5 hours. SCHUBERT & WHITE (1952) injected carrier free ^{212}Pb into rats and detected 17 per cent of the dose in the blood cells at 30 minutes. The rate of loss from the red cell (not including radioactive decay) was 0.0187 per hour for dogs (STOVER) and 0.0231 per hour for rats (SCHUBERT & WHITE). HEVESY & NYLIN stated that in man the loss rate is less than 0.04 per hour.

The data in Table 2 show no consistant loss rate and render unlikely a loss rate greater than 0.007 per hour. If it be assumed for man that the death of the red cell releases the fixed lead and that the lead is removed from the body, for example by secretion in the bile, a minimum release rate can be calculated. Since the average life span of the human red cell is 120 days, the equivalent lead loss rate would be 0.0083 per day or 0.00035 per hour. Neither the data of HEVESY & NYLIN nor our findings can be regarded as excluding this interpretation. On the positive side a test of its feasibility can be applied by using data from the classical lead studies of KEHOE (1943). He found that the daily food intake of stable lead by occupationally unexposed individuals is about 0.35 mg and that the corresponding level in the blood is 0.030 mg per 100 ml. If the blood volume

of an adult is taken as 5 400 ml (ICRP), the total lead burden carried by the blood becomes 1.62 mg. Assuming an average absorption of 8 per cent from the gastrointestinal tract, and that 50 per cent of the absorbed lead is fixed by the blood cells, the daily uptake of lead becomes 0.014 mg. Since the lead concentration in the blood cells must be in a steady state the loss rate constant is 0.014 divided by 1.62 = 0.0086 per day, a value very near to the rate of 0.0083 per day based on the proposal that lead is lost only by death of the blood cell.

If this interpretation is valid it enables a circumstantial statement of the protection against lead poisoning given by the lead fixing property of the red blood cell. The maximum lead binding capacity of the cells can be estimated from the report by KEHOE et coll. (1943). They performed experiments in which two human subjects were given supplementary soluble lead by mouth at the rate of 1 and 2 mg per day over periods of years. From examination of their data it is found that the blood level rises to a mean value of about 0.06 mg lead per 100 ml and does not greatly exceed this. If this concentration represents saturation, the blood cell mechanism could turn over about 0.028 mg lead per day with only transient increases in the plasma concentration. Since by hypothesis the cells are able to pick up only half of the lead introduced from the gut, this would conform to a total systemic intake of about 0.056 mg per day. If the systemic intake exceeds this rate, the average plasma lead concentration must rise. This leads to proportionally increased skeletal deposition and urinary excretion. Toxicity symptoms might be anticipated at plasma lead concentrations up to 4 to 5 times above the unexposed mean levels, on the grounds that equivalent increases in urinary excretion rates have been observed (KEHOE) to be associated with lead intoxication.

Comparison of behavior of carrier free ^{212}Pb and stable lead. In terms of the discussion above, it is apparent that the ^{212}Pb in oral and intravenous administration was no longer carrier free after it entered the gut or the circulatory system. Accordingly, absorption from the gut should not differentiate between ^{212}Pb and stable ions as such. If ^{212}Pb is introduced with supplementary lead in amounts so large as to saturate the binding sites of the blood cells, marked differences in tissue distribution and urinary excretion might be expected.

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SUMMARY

The gastrointestinal absorption of ^{212}Pb by mouth to three human subjects was found to be respectively 1 3 8 1 and 16 0% The absorption was determined by a comparison of the 24 hour urinary excretion of these subjects with the average excretion in th ame period by two subjects who received ^{212}Pb intravenously The only obvious factor related to the wide rang of absorption was that of age increasing age being associated with decreasing absorption The average value of 8% is equal to that used by ICPP It is pointed out that this choice may not be conservative for an appreciable fraction of the population The ^{212}Pb concentrations in the blood cells as a function of time after oral or intravenous administration suggest that lead may be released from the binding *sites only* when the red c ll di s The relationship of this proposal to permissible intakes of stable lead is considered

ZUSAMMENFASSUNG

Bei oraler Verabreichung von ^{212}Pb in drei Personen wurden gastro intestinale Absorptionswerte on 1,3 8 1 und 16 Prozent erhalten Zur Bestimmung der Absorption wurde die 24 Stunden Urinausscheidung dieser Personen mit der durchschnittlichen Ausscheidung *wahrend derselben* Periode in zwei Personen verglichen bei denen *^{212}Pb intravenos* verabreicht wurd Der einzige Faktor der in positiver Korrelation zu dem weiten Absorptions bereich stand war das *Alter mit zunehmenden* Lebensalter nimmt die Ausscheidung ab Der Durchschnittswert von 8 Prozent ist derselbe wie der von ICRP angegebene dieser sollte aber nicht als ausschlaggebend fur einen betrachtlichen Anteil der Bevolkerung betrachtet werden Die Konzentrationen von *^{212}Pb in den Blutzellen* im Verhaltnis zur Zeit nach der oralen oder intravenosen Verabreichung deutet darauf *hin dass* stabiles Blei von den Retensionsstellen nur dann freigesetzt wird wenn die *rote Blutzelle stirbt* Diese Frage wird hinsichtlich der zulassigen Aufnahme von stabilen Blei im Organismus diskutiert

RÉSUMÉ

Après administration *de ^{212}Pb par* voie orale a trois sujets humains on a constate des taux d absorption gastro intestinale de 1 3 8 1 *et 16* % La methode de determination de l absorption a eté de comparer l excretion urinaire de 24 heures de ces sujets avec l excrétion moyenne au cours de la meme *periode de d* ux sujets à qui ^{212}Pb avait ete administre par voie intraveine se Le seul facteur nettement en rapport avec ces taux d absorption très dif ferents est l ge l absorption diminuant quand l age augmente La valeur moyenne *de 8* % est celle qui est donnee par l ICRP Les auteurs soulignent que ce choix ne peut pas convenir pour une partie appreciable de la *population* L etude des concentrations de ^{212}Pb dans les cellules sanguines en fonction du *temps* après administration orale ou intraveineuse fait penser que le plomb ne peut etre libere que quand le globule rouge meurt Les auteurs xaminent les consequences de cette *hypothe* e sur la quantite adm ibl de plomb stable introduit dans le corps

of an adult is taken as 5 400 ml (ICRP), the total lead burden carried by the blood becomes 1 62 mg Assuming an average absorption of 8 per cent from the gastrointestinal tract, and that 50 per cent of the absorbed lead is fixed by the blood cells, the daily uptake of lead becomes 0 014 mg Since the lead concentration in the blood cells must be in a steady state the loss rate constant is 0 014 divided by 1 62 = 0 0086 per day, a value very near to the rate of 0 0083 per day based on the proposal that lead is lost only by death of the blood cell

If this interpretation is valid it enables a circumstantial statement of the protection against lead poisoning given by the lead fixing property of the red blood cell The maximum lead binding capacity of the cells can be estimated from the report by KEHOE *et coll* (1943) They performed experiments in which two human subjects were given supplementary soluble lead by mouth at the rate of 1 and 2 mg per day over periods of years From examination of their data it is found that the blood level rises to a mean value of about 0 06 mg lead per 100 ml and does not greatly exceed this If this concentration represents saturation, the blood cell mechanism could turn over about 0 028 mg lead per day with only transient increases in the plasma concentration Since by hypothesis the cells are able to pick up only half of the lead introduced from the gut, this would conform to a total systemic intake of about 0 056 mg per day If the systemic intake exceeds this rate, the average plasma lead concentration must rise This leads to proportionally increased skeletal deposition and urinary excretion Toxicity symptoms might be anticipated at plasma lead concentrations up to 4 to 5 times above the unexposed mean levels, on the grounds that equivalent increases in urinary excretion rates have been observed (KEHOE) to be associated with lead intoxication

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FROM THE DEPARTMENT OF PHARMACOLOGY ROYAL VETERINARY COLLEGE,
STOCKHOLM SWEDEN

AUTORADIOGRAPHIC STUDIES ON DISTRIBUTION OF RADIOCOBALT CHLORIDE IN PREGNANT MICE

by

HANS FLODH

Cobalt is present in small amounts in all animal material As yet no essential physiological function of cobalt is known except its presence in the vitamin B_{12} molecule

Deficiency symptoms are not known in other animals than sheep and cattle, which need cobalt for their microbiologic synthesis of vitamin B_{12} In large doses cobalt acts upon blood forming organs causing the formation of renal erythropoietin (FISHER et coll 1962) and producing polycythemia (WALTNER & WALTNER 1929 MARSHALL 1935) and hyperglycemia (VON HOLT & VON HOLT 1954 HULTQUIST 1959 BOYD & MACLEAN 1959) Several investigations concerning the metabolism of cobalt have been carried out in recent years using autoradiographic and scintillometric techniques (COMAR & DAVIS 1947 BRAUDE et coll 1949 ULRICH & COPP 1951 MEURMAN & ODEBLAD 1956 CARLBERGER 1961 CARLBERGER et coll 1961 KASANEN et coll 1964) The body distribution of cobalt has been studied in various species e g the rat (CUTHBERTSON et coll 1950 ULRICH & COPP 1951 MEURMAN & ODEBLAD 1956 KASANEN et coll 1964) rabbit (COMAR & DAVIS 1947 VOLK et coll 1953) dog (LEE & WOL

Submitted for publication 14 August 1967

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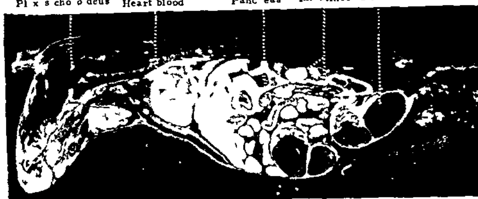


Fig 2 Autoradiogram of ^{60}CoCl in a pregnant mouse 4 hours after intra enous injection The distribut on pattern is similar to that after one hour In addition to the liver and pan creas the e is high concentration in plexus choro deus and costal cartilages

cartilages and fetal skeleton accumulated cobalt to a large extent especially from one day and onwards (Figs 3 and 4) The radioactivity in the fetuses noticeable as early as one hour after the injection (Fig 1) was during the first days selec tively localized to the fetal bones The distribution in different tissue groups at different intervals will be described below

Blood As early as one hour after injection the concentration of radiocobalt in the blood was low Compared to the liver it was about 8 times lower but it was at the same level as in the lungs placentae and salivary glands The activity then gradually disappeared from the blood a process which was largely completed after 24 hours

Cartilage One hour after injection the nasal and costal cartilages of the mother showed high concentration of cobalt By this time radioactivity was also ob servable in fetal bone The concentration of radiocobalt in cartilage increased with time and 4 days after injection it was about 4 times higher than in the liver (Fig 4) From 24 hours after the injection and onwards the cartilages in trachea and larynx of the mother had the highest concentration (Fig 3)

Digestive organs The liver had high concentration of radiocobalt at all times tudied In the pancreas the initial accumulation was at the same level as in the liver the activity then slightly decreased but after 24 hours it was still among the highest in the body One hour after injection the salivary glands had about

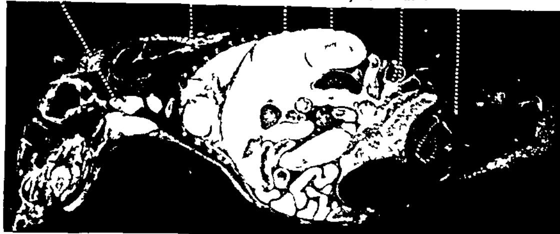


Fig 1 Autoradiogram of $^{60}CoCl$ in a pregnant mouse one hour after intravenous injection The liver pancreas kidneys and mammary glands have the highest concentration Radioactivity already observable in the fetuses is mainly localized to fetal bone

TERINK 1955), sheep (ROTHERY et coll 1953) and cattle (COMAR & DAVIS 1947) In this investigation the distribution in pregnant mice of radiocobalt, $^{60}CoCl_2$, has been studied using whole body autoradiography

Methods Pregnant NMRI mice were intravenously injected with water solutions of $^{60}CoCl_2$ obtained from The Radiochemical Centre, Amersham, England An amount of 0 2 ml, corresponding to a total activity of 10 μCi, was given to each mouse At different times after injection the animals were anaesthetized and immersed into a mixture of solid carbon dioxide and hexane (— 78° C) The times between injection and sacrifice were 1 hour, 4 hours 24 hours, 4 days and 16 days The autoradiographic method has been described by ULLBERG (1954, 1958)

Sagittal 20 μ sections through the whole frozen animals were cut at different levels and dried at — 10° C The films used were Structurix (Gevaert) and Kodirex (Kodak), and the exposure time varied between 2 weeks and 3 months

An isotope staircase, representing known amounts of ^{60}Co in twofold serial dilutions was placed together with the section on some of the films The amount of activity in various tissues could then be compared by densitometry

Results

The highest concentration of radiocobalt in the body was observed in the cartilaginous structures, liver kidneys and pancreas High activity in urinary ways and intestinal contents indicated renal and fecal excretion Maternal

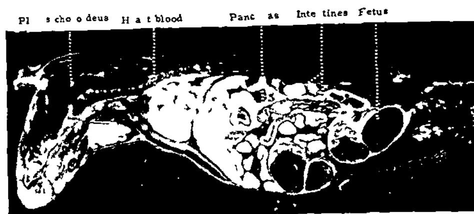


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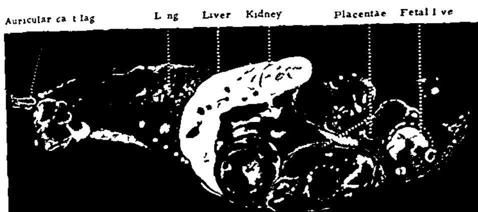


Fig 4 Autoradiogram of ^{60}CoCl in a pregnant mouse 4 days after intravenous injection Cart lages and fetal bone have the highe t concentration Some accumulation may also be seen in the fetal l er

pituitary and thyroid During the first days after injection the adrenal cortex showed higher concentration than the adrenal medulla However, there was a gradual increase in the adrenal medulla which 16 days after the injection had passed the cortex and showed a fairly high concentration (Fig 5)

Central nervous system The uptake of ^{60}Co in the central nervous system was very low throughout the study The choroid plexus however had a high accumulation of cobalt as early as after one hour Four hours after injection it was almost as high as in the liver (Fig 2)

Mammary glands The accumulation of radiocobalt in the mammary glands was high after 24 hours it was at the same level as in the liver and kidneys

Fetus The total fetal accumulation of ^{60}Co at all the intervals studied was lower than that of the dam Some fetal uptake was observable as early as one hour after injection A selective accumulation as high as in the maternal cartilages was seen in the fetal skeleton during the first days after administration There was low concentration in the soft tissues of the fetuses except the liver which showed a fairly high concentration 4 days after injection After 16 days the fetuses had no longer any noticeable radioactivity

Placenta The placenta showed a moderate accumulation of radiocobalt throughout the study with a slight increase during the first 24 hours The radioactivity in the yolk sac epithelium was higher

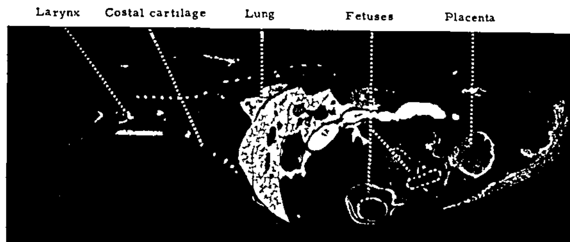


Fig 3 Autoradiogram of $^{60}CoCl_2$ in a pregnant mouse 24 hours after intravenous injection The concentration is very high in maternal cartilages and fetal bone

the same concentration as the blood, placentae and lungs, there were differences between the salivary glands the sublingual salivary gland accumulated more radio cobalt than the submaxillary and parotid salivary glands, with a maximum after 4 days (Fig 4) *The activity in the gastric mucosa and contents was fairly low*, but in the intestinal mucosa and contents there was high activity during the first 24 hours after injection The concentration in the gall bladder did not exceed the blood level

Respiratory organs In addition to the cartilaginous structures cobalt was also to a large extent taken up by the mucous secretion in the respiratory tract In the lungs the accumulation was higher in the bronchioli than in the surrounding lung tissue *The maximum uptake was seen 24 hours after the injection* (Fig 3)

Kidneys The accumulation of cobolt was high in the kidneys with a peak in con centration during the first 4 hours The radioactivity was mainly localized to the inner parts *of the cortex* (Fig 1) *After 4 days the activity was still as high* as in the liver

Myocardium The concentration in the myocardium was fairly low with a relative increase after several days Sixteen days after administration the radio activity in the myocardium was about twice that of the liver (Fig 5)

Endocrine organs The endocrine organs showed fairly low concentrations of radiocobalt The accumulation was a little higher in the adrenals than in the

of cobalt, e.g. mammary glands, salivary glands (mainly the mucous sublingual salivary glands), lingual and palatine mucous glands, mucous secretion in the respiratory ways and mucous and serous membranes in the gastro-intestinal tract. In this respect the distribution of cobalt is similar to that of sulphate, which to a large extent accumulated in cartilages and mucous glands (ULLBERG, unpublished).

The distribution pattern of cobalt was entirely different compared to the pattern obtained in similar autoradiographic investigations with ^{58}CoB$_{12}$ (ULLBERG et coll. 1967). This proved, however, which was expected, that vitamin B$_{12}$ is not metabolized to inorganic cobalt in the body.

Acknowledgement

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SUMMARY

The distribution of ^{60}CoCl in pregnant mice has been studied by whole body autoradiography. The highest accumulation of radiocobalt occurred in the maternal cartilages, fetal skeleton, liver, kidneys and pancreas. Within the fetus the concentration was almost selectively localized to the bone. The mammary glands, salivary glands, placentae, yolk sacs, lungs and intestinal walls and contents also accumulated the isotope, though in smaller degree. The high concentration in cartilaginous structures is discussed.

ZUSAMMENFASSUNG

Die Verteilung des Radiokobalt-Chlorides wurde mittels Ganzkörper-Autoradiographie an trächtigen Mäusen studiert. Bevorzugt wurde Radiokobalt in der mütterlichen Knorpeln, im fetalen Skelet, in der Leber, den Nieren und dem Pankreas abgelagert. Im Fötus war die Aufspeicherung fast ausschliesslich zu den Knochen koncentriert. Radiokobalt wurde auch in den Brust- und Speicheldrüsen, in der Placenta, in den Dottersäcke, Lungen, Darmwände und in dem Darminhalt aufgespeichert, aber nur in geringerem Masse. Die hohe Aufnahme im Knorpel wird diskutiert.

RÉSUMÉ

La distribution du ^{60}CoCl chez les souris gravides a été étudiée par autoradiographie du corps entier. L'accumulation la plus forte de radiocobalt se trouve dans les cartilages de la mère et dans le squelette, le foie, les reins et le pancreas du foetus. Dans le foetus la concentration se localise presque électivement dans l'os. Les glandes mammaires, les glandes salivaires, les placentas, les sacs vitellins, les poumons et la paroi et le contenu de l'intestin fixent aussi l'isotope, à un moindre degré. L'auteur étudie la haute concentration de l'isotope dans les structures cartilagineuses.

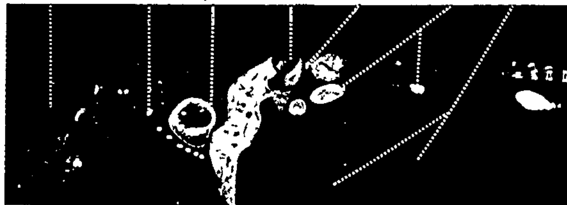


Fig 5 Autoradiogram of ^{60}CoCl in a pregnant mouse 16 days after intravenous injection The concentration in the liver and kidneys has decreased The accumulation is highest in the costal cartilages and the myocardium

Discussion

The present investigation showed a high concentration of cobalt in cartilage as previously described (CARLBERGER 1961) In the adult animals the nasal costal, tracheal and articular cartilages, which are of the hyaline type, and the elastic laryngeal and auricular cartilages accumulated most of the injected radiocobalt chloride The bones of the skull, the periosteum of the vertebrae and the pelvic bone also accumulated cobalt In the fetuses where the radioactivity was almost selectively localized to the fetal skeleton, the uptake was highest in hyaline cartilage of the type that remains as cartilage in the adult animal One exception was the fetal cranial bones which like the cranium of the dam, also showed a high accumulation of cobalt These are the only bones in the body which are formed through intramembraneous ossification The fairly rapid accumulation of cobalt in maternal cartilages and the fetal skeleton is surprising with regard to the absence of blood vessels in these tissues Autoradiographic investigations of the distribution of Na (HUGGERT et coll 1961) and ^{137}Cs (NELSON et coll 1961) have also shown higher accumulation of these elements in cartilage than in other tissues These authors suggested that cartilage may act as cation exchanger and that rapid accumulation in cartilage hardly can be due to incorporation into organic compound Besides the uptake in cartilage there was very little similarity in the distribution between Cs, Na and Co

Cartilage is composed of collagen and chondromucoid There may exist a relationship between the presence of different glucoproteides and the uptake of cobalt since other organs containing these substances also show high accumulation

FROM THE RADIOTHERAPY CLINIC (DIRECTOR PROF S MUSTAKALLIO) OF THE UNIVERSITY CENTRAL HOSPITAL OF HELSINKI FINLAND

EFFECT OF ANATOMICAL IRREGULARITIES ON THE DOSE IN ELECTRON BEAM THERAPY

by

P KARJALAINEN M BRENNER and A RYTILA

Although high energy electrons have been used in therapy for many years little still seems to be known regarding the effect of irregularities of human anatomy on the dose distribution When such irregularities are due to bodies of limited width then perturbations of the normal dose distribution as seen in homogeneous tissue may cause either small areas of overdose (hot spots) or areas of underdose (cold areas) The former may be large enough to damage vital organs or to develop necroses the latter may allow tumour cells to survive treatment and thus lead to recurrence These assumptions have constantly worried therapeutists and physicists To calculate the effect of irregularities by theoretical means seems a tedious approach the effect being dependent on the geometrical dimensions of the perturbing structures The application of the Monte Carlo technique would be a time consuming task even for a single case The present experimental approach is comparable to the investigations of BREITLING & VOGEL (1963) and NETTELAND (1965) but has been accomplished in a way to facilitate the understanding of the effect of irregularities in clinical practice A comparison with the corresponding changes in cobalt therapy has been made

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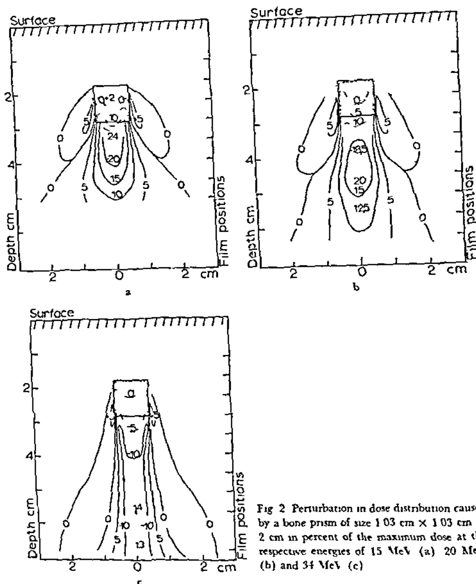
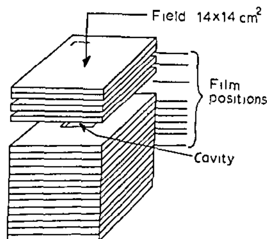


Fig 2 Perturbation in dose distribution caused by a bone prism of size 1 03 cm × 1 03 cm × 2 cm in percent of the maximum dose at the respective energies of 15 MeV (a) 20 MeV (b) and 34 MeV (c)

The resulting density was 1 54 kg/cm³ Bones are actually not homogeneous and for comparison it may be mentioned that the density of the mandible may be of the order of 1 65 g/cm³ (HAAS & SANDBERG 1957)

The perturbation caused by a bone prism of size 1 03 cm by 1 03 cm by 2 cm at primary energies of respectively 15 MeV, 20 MeV and 34 MeV is indicated in



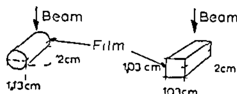


Fig. 1. Polystyrene phantom with a cavity for perturbing bodies (top) and the perturbing bodies introduced in the phantom.

Effects of dense structures. The dose was measured by means of Kodak M radiographic film. This film has a linear density-dose response especially when it is exposed perpendicular to the emulsion plane, which direction was also considered the optimal one for reducing perturbation of the dose distribution from the film itself.

Perturbation of the dose distribution was studied in homogeneous, nearly water equivalent, tissue. The results were made applicable to dose planning by expressing the perturbation in percent of the unperturbed dose at dose maximum. The dose distribution was studied in planes perpendicular to the electron beam at several depths, the films being measured by means of a Joyce double beam micro densitometer. The deviations of the perturbed densitograms from the unperturbed ones were then plotted as illustrated in Figs. 2 to 5.

The films were irradiated in a phantom (Fig. 1) placed between polystyrene slabs with a density, ϱ, of 1.04 g/cm³ and an effective density, ϱ_{eff}, of 0.97 (LOEVINGER, KARZMARK & WEISSBLUTH 1961). A comparison with the corresponding value for perspex (lucite), 1.12, indicates a better equivalency with water.

The perturbing bodies in the soft tissue material (Fig. 1) consisted of bone powder or lead. The bone powder was obtained by milling cattle bones, cooking the powder in water, and drying. The powder was then pressed in steel moulds under high pressure, using a small amount of cellulose lack as binding agent.

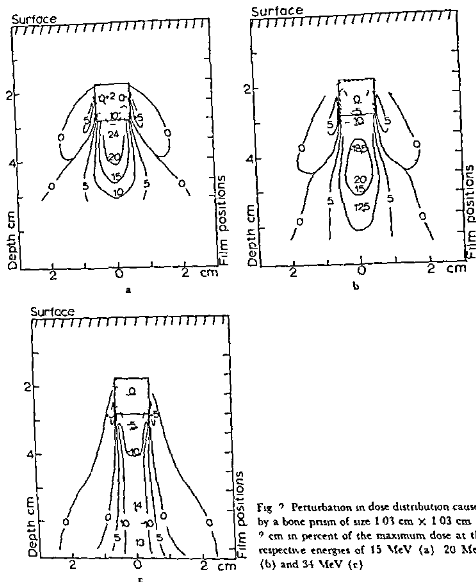


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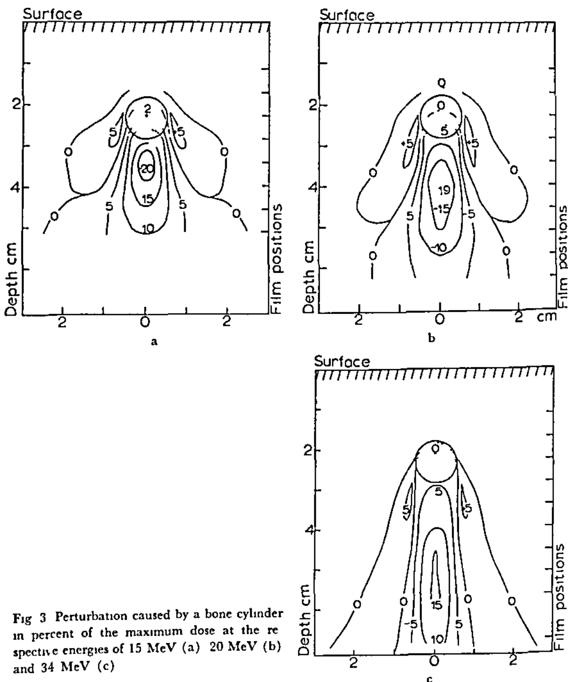


Fig 3 Perturbation caused by a bone cylinder in percent of the maximum dose at the respective energies of 15 MeV (a) 20 MeV (b) and 34 MeV (c)

Fig 2 The distribution is given for a plane cutting the prism perpendicularly in two pieces each of the size 1 cm by 1 cm The influence of the prism seems to result in two areas of perturbation (1) a 'shadow' area, and (2) a side scatter area

The explanation for the appearance of area (1) is simple The radiation

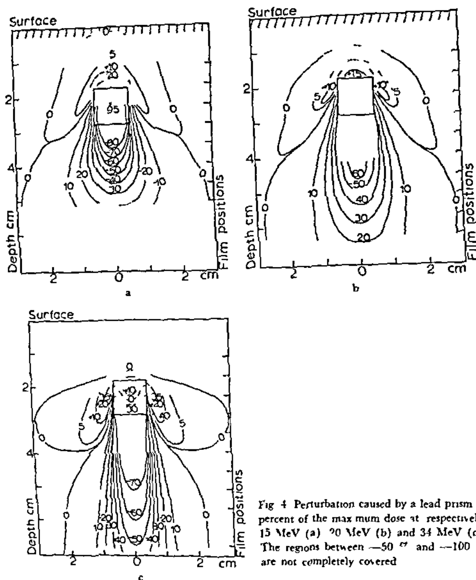


Fig 4 Perturbation caused by a lead prism in percent of the max mum dose at respectively 15 MeV (a) 20 MeV (b) and 34 MeV (c) The regions between —50 % and —100 % are not completely covered

entering from the front face of the piece is absorbed (the particles are more or less arrested) in the piece or scattered from the piece resulting in a shadow' or a cold volume of low dose The effect is well known in roentgen and cobalt therapy

As to the second area of perturbation the radiation scattered from the bone

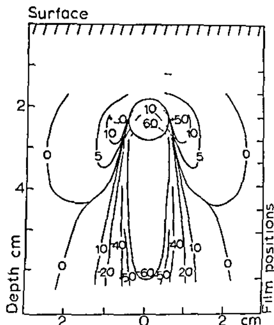


Fig 3 Perturbation caused by a lead cylinder (cf fig 4c)

prism causes an overdose close to the piece This effect is not so marked with roentgen rays and cobalt radiation but in the case of electrons should be considered as a new phenomenon to be taken into account

The overdose value does not change with energy, being always between 5 % and 10 % The underdose, on the contrary, varies between — 20 % and — 14 % when the energy is increased from 15 to 34 MeV With increasing energy, the position of the point of lowest dose moves farther from the piece The volume covered by the shadow reaches far behind the piece at 34 MeV but is shortened at lower energies The underdose becomes more evident at lower energies

The perturbation caused by a cylinder of the same material, volume and cross section as the prism was studied in a corresponding manner The result is recorded in Fig 3 Excepting error of measurement, the perturbation may be considered to amount to the same value as for the prism, the only significant difference being the shapes of the isodoses close to the piece

The dose distribution with a lead prism is given in Fig 4 The electrons do not penetrate the piece at all The underdose behind the prism is thus approximately 100 % at 15 MeV, 20 MeV, and 34 MeV Pure scattering from the soft medium is clearly demonstrated and stands for the dose in the shadow, i e for the difference between the percentage read in the shadow and 100 % perturbation The effect of bremsstrahlung from the piece and the machine should be considered, however, if an exact estimate of the pure scattering effect is to be made The hot spots beside the lead represent a 35 % overdose as com-

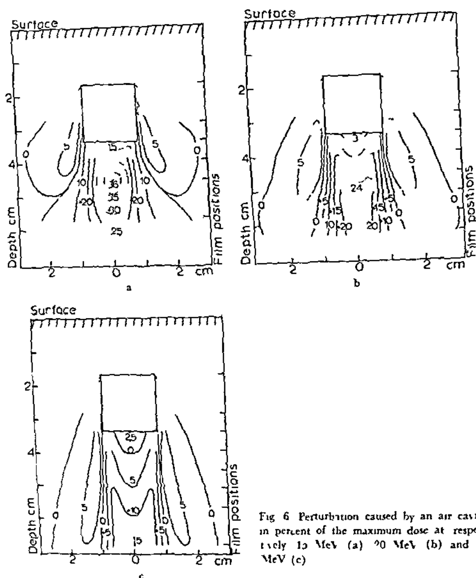


Fig 6 Perturbation caused by an air cavity in percent of the maximum dose at respectively 15 MeV (a) 20 MeV (b) and 34 MeV (c)

pared to only 5 % with bone Moreover the effect of backscattering is considerable at least at low energies The geometrical shape may be of some slight influence when the perturbing body is lead (Fig 5)

Effect of cavities Situations of a cavity perturbing the dose distribution may frequently arise in radiation therapy To simulate the trachea a cavity shaped

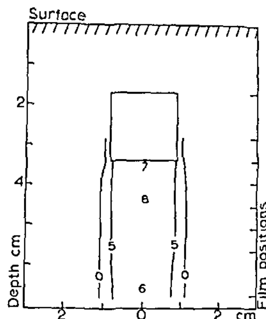


Fig 7 Perturbation at cobalt radiation caused by an air cavity in percent of the maximum dose (cf fig 6)

as a long channel of 2 cm by 2 cm cross section was introduced in a polystyrene phantom Exposure to electrons was performed as previously The phantom was also exposed to a cobalt beam, to provide a comparison between electron and cobalt beam therapy The density was measured by an Ansco Macbeth densitometer The result is illustrated in Fig 6 The perturbation in the two areas is now inverse, compared to the previously investigated conditions There is now a 'positive shadow' (overdose) due to the absence of absorption in the cavity The absence of scattering normally produced by soft tissue (now removed) causes an underdose beside the cavity

No scatter effect at all could be observed with cobalt radiation (Fig 7) The 'positive shadow' is moreover far less marked than that produced by the electrons Its highest isodose is + 35 % at 15 MeV electrons and decreases to + 15 % at 34 MeV The highest value for cobalt is + 8 %

Discussion

Let us now consider the perturbation occurring in the two main cases discussed There are as mentioned two different areas of deviation with different signs These are (1) the shadow that is negative in the first case (underdose) and 'positive' in the second (overdose) and (2) the side scattering area characterized by an overdose in the first and an underdose in the second case

The boundaries of the piece of bone or the cavity define a certain domain in the soft tissue equivalent material It may now be useful to consider the dose as

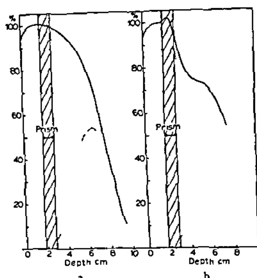


Fig 8 Curves showing the total dose of 20 MeV electrons (solid) unperturbed partial dose (dashed) and zero-perturbed or perturbed dose (dotted) at different depths along the centre line through the domain (a) in a homogeneous phantom and (b) when the domain is filled with the bone prism

caused by two different groups of electrons One group is made up by perturbed electrons i e by primary or secondary electrons having penetrated the perturbing domain or by electrons struck directly or indirectly by them The energy and direction of the perturbed electrons are related to the type of matter (or void) introduced in the domain The other group is represented by electrons not having penetrated the domain and not being secondaries of a first or higher generation to perturbed electrons this group may be called unperturbed electrons The total dose can accordingly be divided into two parts the perturbed and the unperturbed partial dose

The results obtained for lead (Fig 4) enable a study to be made of the unperturbed partial dose at least in the shadow area reached by the unperturbed electrons by scatter from tissue equivalent material surrounding the domain It may be assumed that only a negligible amount of electrons entering the domain will penetrate parts of the lead piece and scatter to the area behind the domain Using a common depth dose curve for 20 MeV and the results of Fig 4b we obtain the curves in Fig 8a which apply to a homogeneous case The solid curve gives the total dose and the dashed curve the unperturbed dose according to Fig 4b The difference between these two curves (shown dotted) represents the dose due to zero-perturbed electrons or that part of the dose which will be affected when the tissue equivalent material that now fills the domain is replaced by matter of different electron density or void It should be pointed out that the curves of Fig 8 are related to a domain with the special

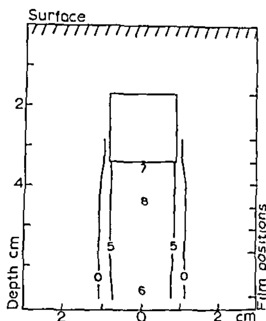


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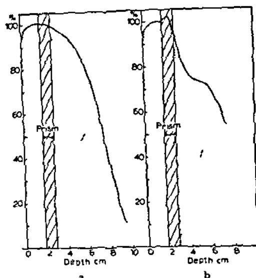


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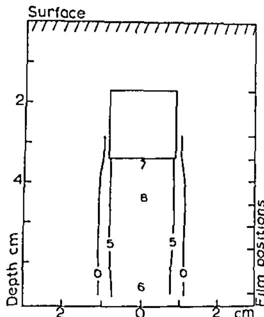


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importance Care should be taken to remember the overdose of 5 % near bone and the underdose of 5 % near a cavity (Figs 2 3 and 6) If lead is to be used as a shield surrounded by tissue the strong side scattering effect should also be born in mind The back scatter in lead is considerable but negligible in bone

It should be mentioned that the perturbation at an air cavity gives when taken with an opposite sign the amount of side scattered electrons from the domain when filled with tissue-equivalent material

It is interesting to consider that the perturbation of the cobalt radiation by a cavity (Fig 7) is much smaller than the perturbation of electrons The same results is expected when bone is used as perturbing body

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SUMMARY

The effect of bone and cavities on the dose distribution of electrons was studied on radiographic film at 15 20 and 34 MeV Bone and lead pieces of two different shapes and a cavity surrounded by polystyrene were used to simulate anatomical irregularities The results were compared with similar measurements for cobalt radiation, and the perturbation for electrons was found to be much greater than for cobalt

ZUSAMMENFASSUNG

Der Einfluss von Knochen und Hohlraumen auf die Dosisverteilung bei Elektronenbestrahlung bei 15 20 und 34 MeV wurde mittels Rontgenfilm studiert und gemessen Knochen und Bleistucke von zwei verschiedenen Formen und eine von Polystyren umgegebenen Hohle wurden verwendet um anatomische Irregularitaten darzustellen Die Resultate wurden mit den Messresultaten bei Kobaltbestrahlung verglichen und es wurde festgestellt dass die Storung bei Elektronenbestrahlung grosser als bei Kobaltbestrahlung war

RÉSUMÉ

L'effet des os et des cavites sur la distribution de dose d'électrons a eté étudié a 15 20 et 34 MeV au moyen de films radiographiques avec des morceaux d'os et de plomb de deux formes differentes et avec une cavité entouree de polystyrène pour simuler les irregularites anatomiques Les resultats sont compares avec ceux de mesures semblables faites pour le rayonnement du cobalt. La perturbation de la distribution de dose est bien plus importante pour les électrons que pour le cobalt

shape of the prism illustrated in Fig 1 Another domain would give curves of different shapes

The dotted curve may be considered a depth dose curve for those electrons that have been influenced by the matter in the domain If matter with a high electron density is introduced, two main effects result The energy of the zero perturbed electrons is reduced, and the scattering is increased to give an ensemble of perturbed electrons The first effect will reduce the range of the curve, and the second will reduce the slope of the curve The combined effect is seen in Fig 8b, where the solid line gives the depth dose curve through the bone prism according to Fig 2b, and the dashed line is the same as in Fig 8a The dotted curve again represents the difference or the dose due to the electrons perturbed by the bone prism The most prominent perturbation of the dose is expected in a region where the zeroperturbed partial dose curve has a steep slope This is illustrated in Fig 8 The increase in the distance between the domain and the position of maximum perturbation with increasing energy is therefore understandable

The perturbation in the shadow area is high enough to be of importance in dose planning This applies to solid bone as well as to cavities A calculation of the perturbation is complicated by two facts First, only a part of the electrons forming the dose is perturbed, as seen above, secondly the depth dose curves of the perturbed electrons depend strongly on the size of the perturbing piece It is evident that the perturbation on the whole does not depend only on the thickness of the domain but also on its width, which defines the ratio of perturbed and unperturbed electrons How complicated the situation may be when planning treatments of the head is obvious Nearly all the electrons are more or less perturbed in some areas when passing bone and cavities of varying thickness and shape It may however be possible to find approximate methods to calculate the dose in areas of such complex structure (LAUGHLIN 1966)

The present results indicate that the maximum value of perturbation decreases with increasing energy This is true for bone and air cavities At lower energies the mean scattering angle is larger, facilitating the scattering of unperturbed electrons on to the shadow area, this is expected to increase the relative importance of the unperturbed electrons in forming the dose at the cost of the contribution of perturbed electrons At lower energies, however, the change in the depth dose curve for the zero perturbed group by the introduction of perturbing matter (or void) will influence an area that lies closer to the domain than the region reached by the bulk of unperturbed electrons The perturbed electrons in this area will dominate the dose to give the more marked perturbation observed at lower energies

The results clearly indicate that the perturbation at the side area is of minor

importance Care should be taken to remember the overdose of 5 % near bone and the underdose of 5 % near a cavity (Figs 2 3 and 6) If lead is to be used as a shield surrounded by tissue the strong side scattering effect should also be born in mind The back scatter in lead is considerable but negligible in bone

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Der Einfluss von Knochen und Hohlraumen auf die Dosisverteilung bei Elektronenbestrahlung bei 15 20 und 34 MeV wurde mittels Rontgenfilm studiert und gemessen Knochen und Bleistucke von zwei verschiedenen Formen und eine von Polystyren umgegebenen Hohle wurden verwend t um anatomische Irregularitaten darzustellen Die Resultate wurden mit den Messresultaten bei Kobaltbestrahlung verglichen und es wurde festgestellt das die Storung bei Elektronenbestrahlung grosser als bei Kobaltbestrahlung war

RÉSUMÉ

L effet de os et des cavites sur la distribution de dose d electrons a éte etudie a 15 20 t 34 M V au moyen de films radiographiques avec d s morceaux d o et de plomb d deux formes differentes et avec une cavité entouree de polystyrene pour simuler les irregularites anatomiques Les resultats sont compares avec ceux de mesures semblables fait s pour le rayonn m nt du cobalt La perturbation de la distribution de dose est bien plus importante pour les électrons que pour le cobalt

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FROM THE DEPARTMENT OF RADIOLOGY, COLLEGE OF MEDICINE UNIVERSITY OF ILLINOIS CHICAGO U S A

THRESHOLD DOSES FOR CONDITIONED AVOIDANCE BEHAVIOR USING LOW DOSE RATE GAMMA RADIATIONS

by

H LeVan R Haas H Sassoon and F Krown

During the past decade many results have been reported on various aspects of postirradiation saccharin aversion in mice It is well known that mice prefer saccharin sodium solution to tap water and avoid this solution after being exposed to ionizing radiations Many techniques have been used with roentgen and gamma rays and fast neutrons (Garcia & Kimeldorf 1960) to condition saccharin aversion No explicit investigations however have been done for threshold doses or dose rates for saccharin aversion conditioning In this paper we are presenting results from our recent studies of some threshold doses using both saccharin and sucrose as the conditioned stimuli and gamma radiations with extremely low dose rates as the unconditioned stimulus

Method Sixty CFW male mice 50 to 60 days old were used The animals were randomly divided into two groups each composed of three cages with 10 mice in a cage and maintained in a controlled temperature room The cages (30 cm long × 20 cm wide × 14 cm high) were made of 3 cm thick lead

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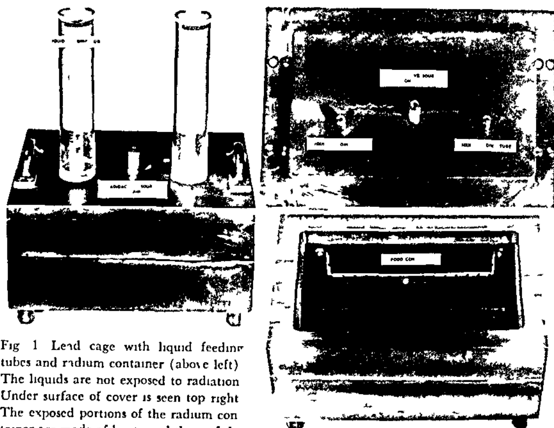


Fig 1 Lead cage with liquid feeding tubes and radium container (above left) The liquids are not exposed to radiation Under surface of cover is seen top right The exposed portions of the radium container are made of lucite and those of the *liquid feeding tubes* are made of *aluminum* Interior view of the cage is seen to the right in the figure

(Fig 1) The removable top of each cage has three holes to accommodate the liquid feeding tubes on the right and the left side, and the radioactive container in the middle The under surface view of the cover is seen to the right in the figure (top) The lucite liquid feeding tubes containing either saccharin *sodium* solution or sucrose solution on one side and plain tap water on the other side were graduated in cubic centimeters These tubes were alternated daily to compensate for any possible positional preference Purina food pellets were available at all times in a food basket mounted inside each cage The bottom of the cage was made of a stainless steel screen for ventilating purpose The cage bottom, supported by four 5 cm high copper legs, was separated from the ground by an air gap Those parts of the liquid feeding tubes that are seen in the figure extend 3 cm into the cage and the part seen of the radioactive source container extends 6 cm into the cage A 5 mg radium capsule was used as source

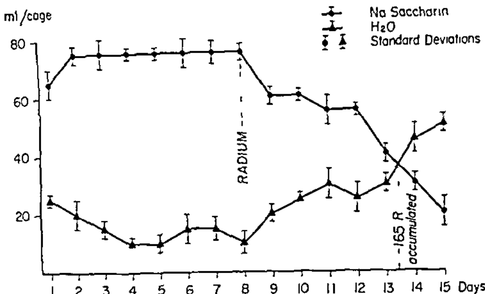


Fig 2 H O nd Na saccharin consumption before and after the introduction of radium source to the cage

Dosimetry was performed using the energy storage and thermoluminescent response of lithium fluoride embedded in a teflon matrix The matrix was formed into a rod 1 mm in diameter and 6 mm in length These rods were embedded under the skin on the back of each mouse before initiation of the preference test and removed for reading when the mouse was sacrificed at the end of the experiment They were then read on a Controls for Radiation Model 5100 Thermoluminescent Reader The resultant doses were averaged to indicate the average total exposure and by inference the average exposure dose rate in the cage The reader and rods were calibrated to read radium gamma exposure rates in air Each experimental part with three cages of mice containing ten each was run under the same conditions except that the liquids used were different saccharin sodium solution (1 % of weight) was offered to the first group and sucrose solution (5 % of weight) to the second After a short period of rest and getting settled in the new environment the mice showed definite preference of either saccarin or sucrose The radium capsule was then inserted into the container The dose rate emitted by this source was approximately 2 1 × 10 R min (at an average distance of 6 cm between the source and the mice)

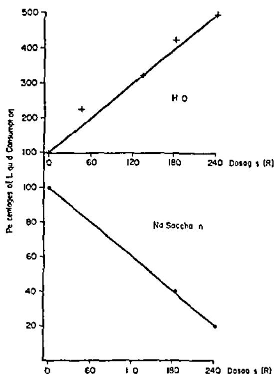


Fig 3 Gamma ray dosages versus percentage of H O and Na saccharin consumption

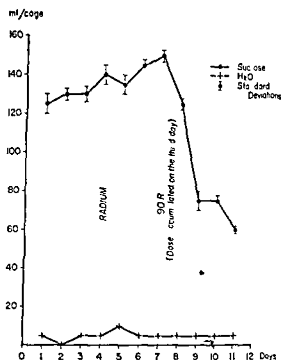


Fig 4 H O and sucrose consumption before and after the introduction of the radium source

Results and Discussion

Saccharin sodium solution was used in the first experimental part Eight days *after the initiation of the taste preference test (Fig 2), the mice definitely pre* ferred this sweet solution to tap water The radium source was then deposited in the container On the following day, the data recorded indicated an average decrease of some 15 ml in the daily amount of saccharin consumed, and an average increase of 10 ml in that of water This trend was observed until between the 13th and 14th day of the experiment (5 5 days after the introduction of the radium capsule) when the average daily water consumption surpassed that of saccharin sodium At this time the mice had been exposed to approximately 165 R of gamma radiations On the 15th day, this experimental part was terminated The average increase in daily water intake was then 40 ml from the time the radium capsule was introduced to the cage The average decrease in daily saccharin consumption was 55 ml lower than at the start The consumption versus average exposure is recorded in Fig 3 Approximately 210 R were ac

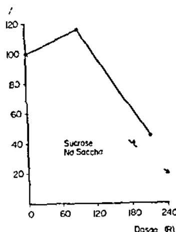


Fig 5 Gamma ray dosages versus percentages of liquid (sucrose and Na saccharin) intake

cumulated during this experiment On the day the radium capsule was introduced into the cage the average daily water and saccharin consumption were scored as 100 % At the end of the experiment the saccharin intake dropped to 20 % while that of water increased to 500 %

As may be seen from the curves the changes in liquid consumption are rather linear It is quite difficult to establish the precise starting point of avoidance of saccharin solution and the accumulated radiation dose at that time In a minute by minute analysis of water and saccharin preferences following simultaneous exposures to saccharin and gamma rays SMITH & SCHAEFFER (1966) found that the aversion started within 15 minutes after exposures We can only say that with the extremely low dose rate used in this experiment the threshold dose for saccharin aversion was much less than 30 R Between the 2nd and the 4th day after the mice were exposed to radiation there was a recession in the daily drop of saccharin consumption perhaps at this low dose rate and after sensing radiation on the 1st day the animals tolerated the new conditions for a while before it became unbearable on the 4th day (150 R accumulated) GARCIA et coll (1955) using saccharin solution (0 1 % of weight) reported that 6 hour exposure to 30 R (^{60}Co/gamma rays) produced a conditioned aversion to saccharin sodium and 57 R produced an absolute rejection of this solution According to SMITH et coll (1964) the duration of exposure for a successful conditioning was about 7 seconds (100 R of roentgen rays) At this rate being well above threshold level these investigators found that the same high degree of aversion was produced (exposure rate was between 100 R to 828 R/min) Our results indicated that at extremely low dose rates (0 02 R/min) 100 R of

gamma radiation produced a drop of some 35 % in the average daily saccharin intake and an increase of 175 % in the daily water consumption.

For sucrose solution (5 % of weight), the results were somewhat different (Fig. 4). The preference of sucrose to water was much higher as compared with saccharin. The same radium capsule was deposited in the container 4 days after the initiation of the sucrose taste preference test. Only neglibible changes were observed in both water and sucrose consumptions on the next day. The mice continued with preference for sucrose solution until the end of the 3rd day, corresponding to an exposure of approximately 90 R. On the next two following days, the average daily sucrose intake decreased by 50 % (from 150 ml to 75 ml). This experiment ended one week after the radium capsule had been introduced into the cage.

Compared to the results obtained in the first experimental part, we found that while the avoidance of saccharin solution was observable within only one day of exposure that of sucrose took much longer. At this extremely low dose rate, the mice avoided sucrose solution only after they had been exposed to 90 R of gamma radiation (Fig. 5). Thereafter, the drop in the percentage of the sucrose consumed was almost linear with the doses accumulated. The average daily intake remained unchanged. Sodium saccharin has been reported to be about 675 times as sweet as sucrose (MONCRIEFF 1944), the solution used in our experiment was then estimated to be about 135 times as sweet as the sucrose solution. This raises a question whether the degree of sweetness of the solution employed is a factor in this conditioned avoidance behavior. Our results seemed to show that the sweeter the solution, the faster could conditioning be produced. It is interesting to note that the average daily water consumption did not change significantly in the sucrose experiment while it appeared to be a linear function of dose in the saccharin experiment.

Acknowledgements

We wish to thank Prof. Roger A. Harvey for his special interest in our project and Prof. Walter S. Moos for his many valuable viewpoints.

SUMMARY

When mice are exposed to low dose rate gamma radiations (2 × 10 R/min) the threshold dose for the conditioned aversion to 1 % saccharin sodium solution is much less than 30 R and for aversion to 5 % sucrose solution is about 90 R. The degree of avoidance changes with the sweetness of the solution and is a linear function of the accumulated radiation dose.

ZUSAMMENFASSUNG

Mause wurden mit sehr niedrigen Dosen von Gammastrahlen (2×10^{-2} R/min) irradiert Die Schwellendosis fur ihre bedingte Aversion gegen eine 1 prozentige Na Saccharinlosung war viel geringer als 30 R und die fur Aversion gegen eine 5 prozentige Saccharose Losung ungefahr 90 R. Der Abstinenzgrad wechselt mit der Susse der Lo ung und ist eine lineare Funktion der akkumulierten Bestrahlungsdosis

RÉSUMÉ

Quand des souris sont exposees a de très faibles débits de dose de rayonnement gamma (2×10^{-2} R/min) la dose seuil pour l aversion conditionnée à une solution de sel de sodium de la sacharine est très inferieure à 30 R, et celle qui conditionne leur aversion pour une solution de saccharose a 5 % est d environ 90 R Le degré d aversion varie avec la doceur de la solution et est une fonction lineaire de la dose totale de rayonnement

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UNIVERSITY OF LUND, SWEDEN

HUMAN RADIUM ASSAY AT NANOCURIE LEVELS USING EXTERNAL COUNTING OF LOW ENERGY PHOTONS

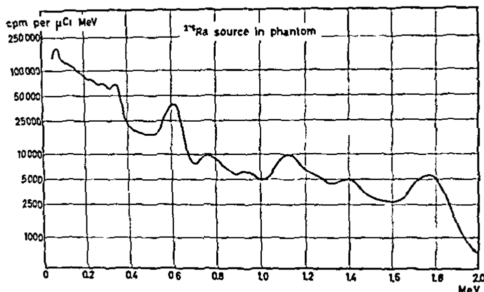
by

L. G. BENGTSSON

Many gamma rays are emitted in the decays of ^{226}Ra and its daughters. When these nuclides are present in a human subject, the gamma rays, as measured by whole body counting, will be distorted by scattering and absorption within the human body. As a result, the spectrum obtained will be very complex and similar to the spectrum in Fig. 1. This spectrum was obtained from measurement of a ^{226}Ra source in the middle of a masonite phantom, using a NaI(Tl) crystal. There are some prominent peaks in this spectrum which are often used for detection of radium in man, especially the one around 1.76 MeV (EVANS 1965, PSZONA, ADAMSKA & ZARNOWIECKI 1963, WENGER & MILLER 1963). In the present investigation it has been found that the low energy region of the spectrum may also be used to advantage for detection of radium in man. This article thus presents one of several attempts made by whole body counting investigators in recent years to make more efficient use of the information contained in the entire spectrum (MCNEILL & MOHINDRA 1964, LILLEGRAVEN & RUNDO 1965, BENGTSSON 1964).

An indication of the usefulness of the various energy ranges of radium spectra for an assay of small amounts of radium has been obtained from a consideration

Submitted for publication 18 April 1967.



F g 1 Spectra f om a masonite phantom contain ng a Ra source Scanning bed geometry and *20 cm 20 cm NaI (Tl) crystal*

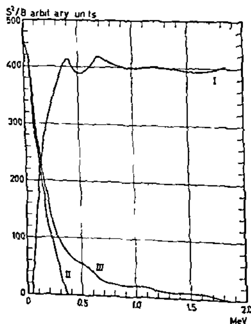


Fig 2 F gure of statist cal merit S /B (the same arbitrary un ts s n Table 1) for the va ious parts of a spectrum similar to the *rad um spectrum obtained in* man S /B was calculated for energy anges w th on l m t f xed and the oth r set as *ind cated by the reading on the horisontal* ax s The energy r nges are then I—lower limit 0 04 MeV upper l mit variable II—*lower l mit var able upper limit 0 38* MeV III—lower l mit ar able upper limit 1 82 MeV

Table 1

Influence of the chosen energy range on the counting statistics for assay of small amounts of radium in an otherwise radioactivity free subject (Compare also Fig 2) S = counting rate from radium, B = background counting rate figure of merit S²/B (the same arbitrary units as in Fig 2)

Principal gamma energy MeV	Energy range MeV	S²/B arbitrary units	Minimum detectable amount of radium relative to energy range 0 04 to 0 38 MeV
—	0 04—0 38	410	1
0 609	0 52—0 72	30	3 7
1 12	1 02—1 18	7	7 6
1 76	1 60—1 82	10	6 4

of counting statistics There are some differences between the phantom spectrum in Fig 1 and the spectrum from ^{226}Ra in man because of the disequilibrium with the daughter products in the latter case (about 2/3 of ^{222}Rn escape from the body) and because of the self absorption of soft gamma rays in bone The results derived from the statistical considerations below will only in details be influenced by such differences The statistical merit for various energy ranges has been calculated for spectra similar to the one shown in Fig 1 As a figure of merit S^2/B has been used, where S is the net counting rate from radium and B is the background counting rate This figure of merit applies to the hypothetical case of a subject free of any radioactivity other than an amount of radium so small that S will be much smaller than B Results from the calculations are given in Fig 2 and Table 1 Some care should be exercised in the application of these results to man because the spectrum below 100 keV may vary considerably, among other things because of the absorption in bone of the low energy gamma rays It is nevertheless quite evident that the statistical merits of the low energy region of the spectrum are considerable Much smaller amounts of radium can be detected than by the use of the higher peaks for the hypothetical situation treated

Man is in fact not free from radioactivity but contains various radionuclides, mainly ^{137}Cs from fall out and a natural potassium burden including ^{40}K The total counting rate from these radionuclides in the low energy end of the spectrum is of the same order of magnitude as the background counting rate For some parts of the spectrum S^2/B as given in Fig 2 and Table 1 would then be changed by about a factor of 2 for a subject containing about 15 nCi ^{137}Cs and 100 g potassium, but the advantages to be expected from use of the low

energy region would persist The possible usefulness of the suggested low energy region is however limited by the accuracy with which we can account for the contributions from ^{137}Cs and potassium in the individual case In fact since the background in the low energy region varies with the size of the subject we must also be able properly to estimate the contribution from the background to the subject s gross spectrum The treatment of these problems is described below

Equipment and Methods The whole body counter in these measurements has been described in the Directory of Whole Body Radioactivity Monitors (IAEA 1964) The scanning took place in a steel room using a NaI(Tl) crystal of 20 cm diameter and 10 cm length with 45 cm bed crystal distance and a scanning length of 144 cm The subject is as a rule measured 19 min in the prone as well as 19 min in the supine position The average result from the two measurements has been used in this work Pulse height spectra were recorded with a 200 channel analyser (RIDL model 34 8) and punched on paper tape Computations were made on the SMIL computer at Lund

The experimental work has proved the necessity of taking utmost care to avoid disturbances from various sources Each subject had a shower and a hair wash before each measurement and was dressed in a cotton overall during the measurement The overalls were checked for activity content and only uncontaminated overalls were used Measurements of the background were performed before and after each measurement in the subject, and significant changes were found in the low energy region of the background spectra These changes seemed to be slow and it took hours before they appeared or disappeared The door of the steel room was only left open for passage in and out which may have served to diminish the variations

Calibration studies of the influence of body weight on the spectra from ^{137}Cs and ^{40}K have been reported by BENGTSSON (1964) A linear relation was assumed to exist between the ratio (low energy band counting rate)/(peak counting rate) and the body weight A linear relation was also found for the dependence of the background in the low energy band on body weight An estimate of the sensitivity for radium distributed in the skeleton was made through calibration studies of a ^{226}Ra source in different positions in masonite phantoms of varying size and shape This estimate proved to be in reasonable agreement with the results from other laboratories in an intercomparison study of two subjects containing ^{226}Ra (WENGER BENGTSSON DUDLEY et coll) It is important to note that the source (NBS standard source No 4956) contained ^{226}Ra in solution in a sealed ampoule For the low energy end of the spectra the usual platinum encapsulation of radium sources caused heavy absorption and even

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Influence of the chosen energy range on the counting statistics for assay of small amounts of radium in an otherwise radioactivity free subject. (Compare also Fig. 2.) S = counting rate from radium, B = background counting rate, figure of merit S^2/B (the same arbitrary units as in Fig. 2)

Principal gamma energy MeV	Energy range MeV	S^2/B arbitrary units	Minimum detectable amount of radium relative to energy range 0.04 to 0.38 MeV
—	0.04—0.38	410	1
0.609	0.52—0.72	30	3.7
1.12	1.02—1.18	7	7.6
1.76	1.60—1.82	10	6.4

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Table 2

Detectability of radium according to measurements on subjects containing 70 to 160 g of potassium and 5 to 20 nCi ^{137}Cs. The subjects were each measured 38 min. Background was measured during 38 min before and 38 min after the subject measurement. SD = standard deviation

Criterion for detectability	Detectable* Bi nCi		nCi Bi corresponding to observed average rest	
	Using 0.04 to 0.40 MeV	Using 1.60 to 1.83 MeV	0.04 to 0.40 MeV	1.60 to 1.83 MeV
3 SD from counting statistics	1.0	2.9		
3 SD from observed rest counting rate all weights (20 subjects)	1.6	2.9	1.0	0.5
3 SD from observed rest counting rate weight 53–67 kg (8 subjects)	1.1	1.3	0.8	0.5

0.1 nCi ^{226}Ra which gives 1 cpm). For comparison the corresponding data for the energy range 1.60 to 1.82 MeV is given in Fig. 3b.

The magnitude of the rest counting rate is however less interesting than the fact that the spread of the individual rests about the average rest value is not much greater than that which could be expected from counting statistics (see Table 2). This means that there should be an advantage using the low energy band to decide which people have a radium burden below the detectable. This was also demonstrated through measurements of two subjects contaminated with small amounts of radium (BERG, KRISTENSEN, GRANDE & MADSEN 1966). These subjects were measured in chair geometry four times with approximately half year intervals. Their radium contents could be predicted from the chair geometry retention curves when they were too small to be measured from the 1.76 MeV peak. This peak, like most gamma rays, does in fact originate not from ^{226}Ra but from ^{214}Bi which is a decay product in the ^{226}Ra series. There is one weak gamma ray from ^{226}Ra at 0.19 MeV which should contribute about 10 per cent of the total counting rate in the range 0.04 to 0.40 MeV. For this application it can be disregarded and what is really assayed by gamma spectrometry is thus ^{214}Bi and other ^{226}Ra series nuclides in equilibrium with ^{214}Bi so body burdens are given for ^{214}Bi only. The ^{226}Ra body burden is usually three times higher than the ^{214}Bi burden. The relevant results of measurements of radium contaminated subjects are given in Fig. 4. The histograms from Fig. 3 have been reproduced on the axes for rest counts.

For detection of small amounts of radium in a control group we should specify a detection level of rest counting rate. Subjects with rest counting

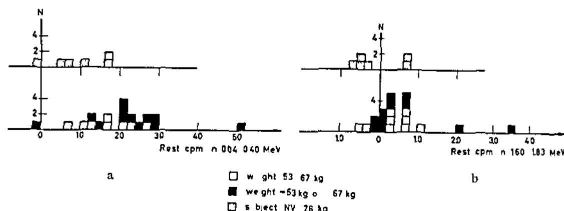


Fig 3 Frequency distributions of rest counting rates for 38 min measurements in 20 normal subjects and for six 38 min measurements in subject N Y N = number of subjects with rest counting rate within a given interval a) Low energy band 0 04 to 0 40 MeV b) 1 76 MeV peak 1 60 to 1 83 MeV

the available radium sources on thin silver foil (Amersham RAM 2) were not suitable for the calibrations because of too high absorption in the silver

The evaluation of the usefulness of the low energy range for the assay of radium in human subjects has been made in two ways

1 It is possible to extend the common procedure for assay of ^{137}Cs and potassium in human subjects to include a detection procedure for radium Additional to the ^{137}Cs and potassium energy ranges, a low energy range is included In this energy range, the individual s contributions from the ^{137}Cs and potassium energy ranges are subtracted using a spectrum stripping procedure If the remaining rest is too large, a further investigation may reveal whether the rest is caused by radium

2 When it is known that a radium contamination is present, the calculations include also the contributions from radium in the ^{137}Cs and potassium energy ranges

Results

1 *No radium contamination assumed* A group of subjects from Lund (55 7 N, 13 2°E) were measured and the results from the calibration studies were used to subtract from each subject s gross spectrum the contributions in the low energy band (40 to 400 keV) from his ^{137}Cs, ^{40}K and background On the average, the rest obtained (Fig 3a) was a little more than zero This may be due to inaccurate corrections for the various contributions in the gross spectrum, and also to small amounts of unknown radioactivity (for instance adult Swedish subjects should contain about 1 nCi ^{90}Sr which gives 0 6 cpm, and

Table 2

Detectability of radium according to measurements on subjects containing 70 to 160 g of potassium and 5 to 20 nCi ^{137}Cs. The subjects were each measured 38 min. Background was measured during 38 min before and 38 min after the subject measurement. SD = standard deviation

Criterion for detectability	Detectable Bi nCi		nCi Bi corresponding to observed average rest	
	Using 0.04 to 0.40 MeV	Using 1.60 to 1.83 MeV	0.04 to 0.40 MeV	1.60 to 1.83 MeV
3 SD from counting statistics	1.0	2.9		
3 SD from observed rest counting rate, all weights (20 subjects)	1.6	2.9	1.0	0.5
3 SD from observed rest counting rate, weight 53—67 kg (8 subjects)	1.1	1.3	0.8	0.5

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For detection of small amounts of radium in a control group we should specify a detection level of rest counting rate. Subjects with rest counting

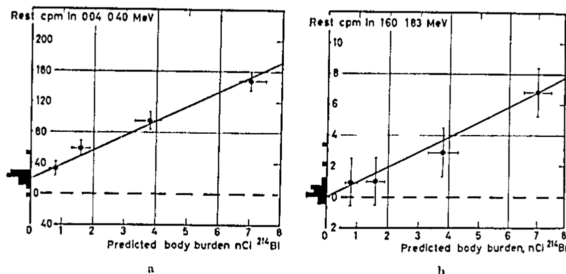


Fig. 4. Rest counting rates for two subjects with slight contamination of radium. Calculation was made as in fig. 3. Bars indicate ± 2 SD. a) Low energy band 0.04 to 0.40 MeV. b) 1.76 MeV peak 1.60 to 1.83 MeV. The subjects were measured in the scanning bed geometry.

rates below this level should be assumed to have no detectable radium content. Those having a rest counting rate above the specified level should be assigned a radium content and this content should be checked by further measurements. The choice of the detection level is somewhat arbitrary. Whether we chose for this level the average rest value plus three standard deviations expected from counting statistics or plus three standard deviations as estimated from the spread of the observed rest values, comparison of the two energy ranges shows that the detectability is better by a factor of between 2 and 3 for the low energy range (Table 2).

The rest counting rate in the low energy range was 50 cpm for one subject (Fig. 3a), although the counting rate in the 1.76 MeV energy range was negative. This subject was remeasured after one month. The rest counting rate in the low energy range was this time 10 cpm which is more consistent with the distribution of the other rest values in Fig. 3a.

The spread of the observed rest counting rate is apparently reduced if the weights of the subjects are restricted to a narrow weight range. This might be due to a more correct subtraction of contributions from ^{137}Cs and potassium for these weights (the Alderson phantom used for medium weights might be more reliable than the home made bottle phantom used for higher and lower weights (see BENGTSSON 1964). However, it may be doubtful to sub group results from only 20 cases, and for the energy range 1.60 to 1.83 MeV, the results from the medium weight group happen to be far too well gathered.

Table 3

Comparison of results from assay of small human body burdens of ^{214}Bi using an energy range between 0 04 and 0 40 MeV and an energy range around the 1 76 MeV peak (1 60 to 1 82 MeV) Subjects were measured 76 min and background was measured 38 min before and 38 min after the subject measurement SD stat = standard deviation from counting statistics SD syst = estimated systematic standard error from calibration uncertainties

Subject cod height and weight	Date of measurement	Energy range 0 04 to 0 40 MeV			Energy range 1 60 to 1 82 MeV		
		Body burden	nCi ^{214}Bi		Body burden	nCi ^{214}Bi	
			SD stat	SD syst		SD stat	SD syst
HP	16 11 65	6 4	0 23	0 29	6 5	0 83	0 23
156 cm							
57 kg	20 7 66	3 7	0 22	0 17	2 7	0 80	0 09
IM	16 11 65	2 0	0 22	0 09	1 0	0 78	0 04
160 cm							
63 kg	20 7 66	1 1	0 20	0 05	0 9	0 78	0 03

2 *Radium contaminated subjects* It should be observed that for the type (1) analysis of the subjects containing radium no assumption was made concerning radium content Thus the counts from radium in the cesium and potassium peaks were treated as had they been due to these latter nuclides There is consequently a loss of information which contributes to the impairment of the statistical merit discussed on page 150 Some of this merit can be regained if we approach the problem of estimating the contamination of a subject, knowing that he has a radium content In this case the contributions in the cesium and potassium ranges are made equal to zero and those in the low energy band are equalled to the average rest for normal subjects From the results given in Table 3 it is apparent that the statistical accuracy for low radium contents is much improved by use of the low energy band Instead however the systematic errors due to variations in the shape of the human radium spectrum are somewhat larger than for the high energy band These errors have been estimated from phantom measurements A further source of error is the uncertainty of the true rest counting rate We may assume that the observed individual rest counting rates are the result of counting statistics variations around one common rest counting rate For the whole normal group this common rest counting rate in the energy range 0 04 to 0 40 MeV then corresponds to 1 0±0 1 nCi ^{214}Bi For the intermediate weight group the corresponding figure is 0 8±0 1 nCi In each case the standard error of the mean rest counting rate thus corresponds to 0 1 nCi ^{214}Bi For the energy

range 1 60 to 1 82 MeV the corresponding figure is 0 2 nCi ^{214}Bi The assumption used is not self evident for the energy range 0 04 to 0 40 MeV, but can only be checked through measurement of a considerably larger control group

Discussion

The content of ^{226}Ra in man on the average amounts to less than 0 1 nCi (STEHNEY 1960) This content originates from the intake of radium through various channels There are large variations in the naturally occurring radium levels, for instance in drinking water As a consequence, individuals exist with natural body burdens slightly smaller than 1 nCi ^{226}Ra (STEHNEY) and even higher body burdens may be possible The limit of detectability of ^{226}Ra in humans is with conventional whole body counting methods very approximately 5 *nCi* (EVANS 1965, *PSZONA et coll* 1963, *MUTH* & *OBERHAUSEN* 1964, VENNART, MAYCOCK, GODFREY & DAVIES 1964, BOULENGER, COLARD & HENRY 1962) Natural radium burdens could probably be detected by means of whole body counting in an increasing number of people if this limit were lowered

The results of the present work show that the detectability of radium in individuals with cesium body burdens up to about 20 nCi ^{137}Cs can be improved by about a factor of 2 by use of the energy band from 40 to 400 keV as compared to a band covering the 1 76 MeV peak The accuracy for assay of small amounts of radium can also be improved in this way but the results do not allow conclusions as to the exact magnitude of the improvement The comparison has not been made for the prominent 0 61 MeV radium peak which lies so close to the 0 66 MeV ^{137}Cs peak that the systematic errors associated with its use would be severe

It should be observed that these measurements are made in scanning geometry where the spectral variations from subject to subject should be easier to evaluate than, for instance, in the more sensitive chair geometry However, results from analysis of chair geometry measurements indicate that the improvement may persist also for this geometry (DEVELL, VENNER and MANDAHL 1966)

Acknowledgement

The author wishes to thank Professor Kurt Liden for his advice and encouragement during this investigation

SUMMARY

The sensitivity of whole body counting (NaI(Tl)crystal) for assay of small amounts of ^{226}Ra can be increased by special use of the low energy part of the spectrum For normal subjects the minimum detectable amount of the ^{226}Ra daughter ^{214}Bi can be improved by

about a factor of 2 This was verified from measurements of both 20 normal subjects containing besides potassium also 5 to 20 nCi ^{137}Cs and two subjects containing also 1 to 6 nCi ^{214}Bi (normally equivalent to about 3 to 20 nCi ^{226}Ra) Since the identification obtained from the low energy part of the spectrum is poor the main use of the method will be for sorting out members of a given group not containing any detectable amounts of radium

ZUSAMMENFASSUNG

Die Empfindlichkeit eines Ganzkorperzahlers zum Nachweis geringer Mengen von ^{226}Ra kann durch eine spezielle Auswertung des niederenergetischen Teils des Spektrums verbessert werden Fur den Normalmenschen wird der minimale anzeigbare Betrag des Tochterproduktes ^{214}Bi von ^{226}Ra um einen Faktor 2 herabgesetzt Das wird sowohl durch Messungen an 20 Normalmenschen die neben K ebenfalls 1—6 nCi ^{137}Cs enthielten bestatigt als auch an 2 Personen die ausserdem noch einen Gehalt von 1—6 nCi ^{214}Bi (normalerweise aquivalent 3—20 nCi ^{226}Ra) hatten Da die Identifizierung mit Hilfe des niederenergetischen Teils des Spektrums schlecht ist ist die Methode hauptsachlich dafur geeignet aus einer Gruppe von Menschen solche auszusondern die keine nachweisbaren Mengen von Ra enthalten

RÉSUMÉ

La sensibilité du comptage corporel total (cristal de NaI(Tl)) pour la mesure de petites quantités de ^{226}Ra peut être augmentée si on utilise spécialement la partie du spectre qui a une faible énergie Pour les sujets normaux la plus petite quantité décelable de ^{214}Bi élément fils de ^{226}Ra peut etre réduite environ par un facteur 2 Ceci a été vérifié par des mesures effectuées sur 20 sujets normaux contenant outre de potassium de 5 à 20 nCi de ^{137}Cs et sur deux sujets contenant aussi de 1 à 6 nCi de ^{214}Bi (équivalent normalement à 3 à 20 nCi de ^{226}Ra) Etant donné que l identification par la partie du spectre qui a une faible énergie est mauvaise la principale utilité de cette méthode sera de reconnaitre dans un groupe donné les sujets qui ne contiennent pas de quantité décelable de radium

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CYTOPLASMIC ULTRAVIOLET EXTINCTION OF STRONTIUM 90 INDUCED FIBROBLASTIC OSTEOSARCOMAS CORRELATED TO HISTOLOGIC APPEARANCE AND ULTRASTRUCTURE

by

PAR SUNDELIN and AGNAR NILSSON

The development of ^{90}Sr induced fibroblastic osteosarcomas through different morphologic stages of oncogenesis and the histologic appearance of overt tumours have been well established in mice (NILSSON 1962 NILSSON & ULLBERG 1962) The present study is concerned with the general histology of ^{90}Sr induced tumours and the question whether they follow the general tumour pattern, with correlation between cytoplasmic RNA active cell proliferation and the histologic and clinical signs of malignancy (AMBS & THORELL 1959 CASPERSSON & SANTESSON 1942 MOBERGER 1954 MOBERGER et coll 1952 THORELL 1947) This has been investigated histologically by ultraviolet cytophotometry and by electron microscopy of ^{90}Sr induced tumours

Material and Methods

Male CBA mice 75 days old were injected intraperitoneally with ^{90}Sr corresponding to 0 7 to 0 8 μCi/g bodyweight The mice weighed between 22 and

From the Department of Pathology (Director Prof B Thorell) Karolinska Sjukhuset Stockholm and the Division of Radiobiology (Director Docent A Nelson) the Research Institute of National Defence Sundbyberg Sweden Submitted for publication 10 November 1967

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Material and Methods

Male CBA mice 75 days old were injected intraperitoneally with ^{90}Sr corresponding to 0.7 to 0.8 μCi/g bodyweight. The mice weighed between 22 and

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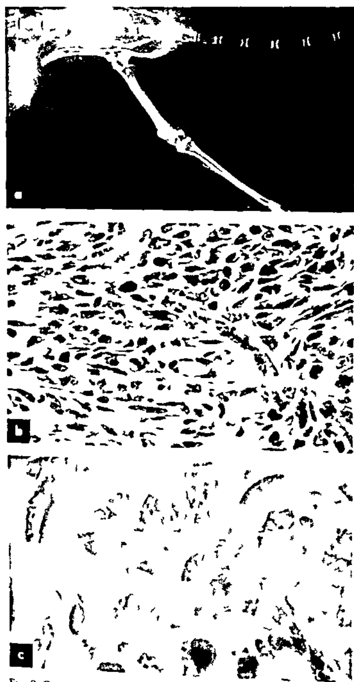


Fig 2 Group 4 Intramedullary tumour in right femur 269 days after administration of ^{90}Sr a) Roentgenogram b) van Gieson ×500 c) Ultraviolet × 1000

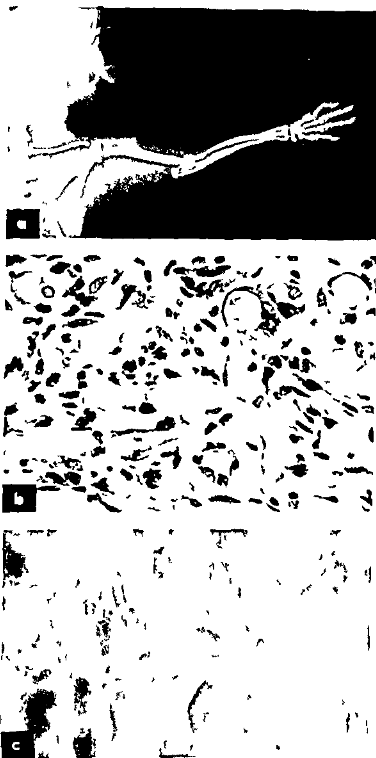


Fig 1 Group 3 Tumour from left humerus 276 days after ^{90}Sr injection Proliferation of reticular cells and pleomorphism a) Roentgenogram b) van Gieson ×500 c) Ultraviolet ×1000

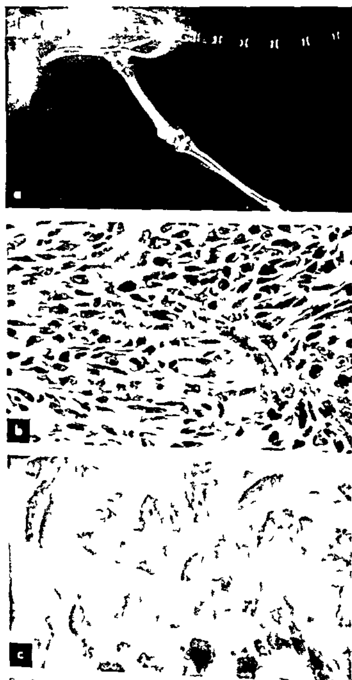


Fig 2 Group 4 Intramed llary tumour in right femur 269 days after admin tration of S a) Roentgenogram b) van Gieson ×500 c) Ultra iolet × 1000

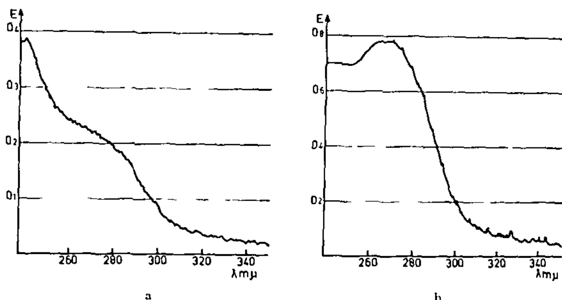


Fig 3 Ultraviolet extinction spectrum of cytoplasm a) Reticular cell with normal structure b) Tumour cell group 4 A specific nucleic acid absorption peak is visible

23 grams initially and were fed and kept under constant conditions before being killed at intervals between 190 and 377 days after the ^{90}Sr injection

For the histologic study, bone tissue were fixed in 5 % neutral formalin for 6 hours rinsed in tap water for 24 hours and decalcified under vacuum in 20 % formic acid for 3 hours, dehydrated, embedded in paraffin and sectioned at 5 μ All sections were stained by van Gieson s method

All the tumours used for this study were predominantly fibroblastic osteosarcomas with scanty osteoblastic elements and little osteoid formation The ultraviolet analysis was performed on cells with evident fibroblastic character

The material could be classified by the microscopic appearance of the reticular cells in the bone marrow into nine stages of tumour development Group 0 represented hypoplastic bone marrow with morphologically normal reticular cells and group 1 aplastic bone marrow with swelling and increased number of reticular cells In group 2 there was a distinct proliferation of reticular cells but the tissue had the histologic appearance of fibrosis without neoplastic character Group 3 (Fig 1), group 4 (Fig 2) and group 5 represented tumours situated completely within the bone marrow The different groups were distinguished by the size of the tumour, cellularity and pleomorphism Groups 6 to 8 consisted of tumours infiltrating and breaking through the compact bone and infiltrating the sur

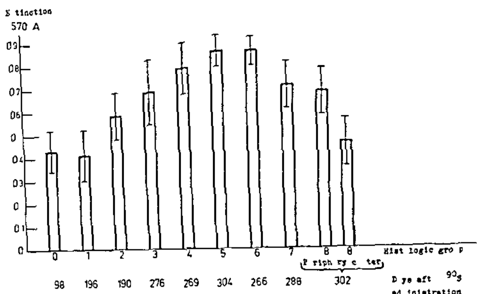


Fig 4 C toplasmic extinction in cells from ucce ively more ad anced tumours (see text) Each column repre ents mean value for 20 cells and standard deviation

rounding soft tissue The main differences between groups 6 7 and 8 were suc cessively increasing cellularity and size

The femurs collected for electron micrography belonged to the histologic groups 0 2 5 and 8 The material was fixed in Os₄ embedded in epon and sectioned with an LKB ultratome with a glass knife stained with lead citrate and examined in a Siemens Elmiscop IA

For the ultraviolet microphotometry paraffin sections 3 μ thick were de paraffinized in chloroform placed on quarz slides immersed in glycerol for 2 days and mounted in glycerol Cytoplasmic areas of fibroblastic cells were analysed in a UV spectrophotometer (CHANCE et coll 1959) by recording con tinuous spectra from 240 to 350 mμ The instrument was used in the present in vestigation with a Zeiss UV achromat condensor stopped down to NA 0 4 and ultrafluar objective NA 0 85 In the cytoplasm of tumour cells a specific ab sorption peak could generally be registered close to 260 mμ In apparently normal fibroblasts this peak was lower or could not be detected at all (Fig 3)

An estimate of the RNA contribution to the absorption at 260 mμ was ob tained by recording the absorption before and after digestion and extraction of the RNA Digestion was done with 1 % RNase at 37° C for 60 minutes and

Table

Percentage reduction of cytoplasmic extinction values of group 5 tumour cells after digestion with RNase and extraction with perchloric acid Γ_{2570}

Before digestion	After digestion	Percentage reduction
0.75	0.56	29
0.76	0.42	45
0.76	0.40	47
0.76	0.47	39
0.64	0.33	48
0.23	0.12	48
0.70	0.41	44
0.48	0.23	52
0.46	0.22	48
0.43	0.31	28
0.38	0.22	42
0.60	0.30	50
0.43	0.32	26
0.57	0.42	26
0.58	0.37	36
0.84	0.46	45
0.40	0.24	40
0.49	0.36	26
0.51	0.35	31
0.57	0.33	42
0.85	0.43	51
0.53	0.30	43
0.41	0.25	39
0.50	0.27	46
0.48	0.28	41
		Mean ± SD 40 ± 8

extraction with 1 % perchloric acid at 4° C for 20 minutes followed by rinsing in water for 2 hours (PERRY et coll 1961) Identical points in the cytoplasmic areas were measured according to THORELL (1947) before and after digestion and extraction in phosphatic buffer saline pH 7.2

Results and Discussion

The tumours will be considered here solely in relation to their histologic appearance and not in relation to their induction time since these are not necessarily correlated with each other



Fig 5 Group 8 Tumour cell with abundant rough endoplasmic reticulum and aggregation of ribosome × 54 000

Digestion with RNase indicated that about 40 % of the cytoplasmic ultra violet extinction values were attributable to RNA (see Table) The values could clearly be correlated to the histologic groups (Fig 4) The morphologically more advanced stages of intramedullary tumour development were associated with increasing extinction values The extramedullary tumour cells however had lower extinction values than the peak values obtained for intramedullary tumours In overt tumours the cells towards the periphery also contained apparently greater amounts of cytoplasmic RNA than those in the center (cf CASPERSSON & SANTESSON 1942)

The cytoplasmic ultraviolet extinction reflects both ribosomal and soluble RNA The ribosomal fraction can be further analysed with the ultrastructural technique

The electron micrographs revealed no significant differences between normal reticular cells and group 2 tumour cells while the established tumour cells had some significant alterations

The ribosomes were generally much more abundant in cells from established

Table

Percentage reduction of cytoplasmic extinction values of group 5 tumour cells after digestion with RNase and extraction with perchloric acid E_{260}

Before digestion	After digestion	Percentage reduction
0.75	0.56	29
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0.76	0.40	47
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0.64	0.33	48
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0.48	0.28	41
	Mean ± SD	40 ± 8

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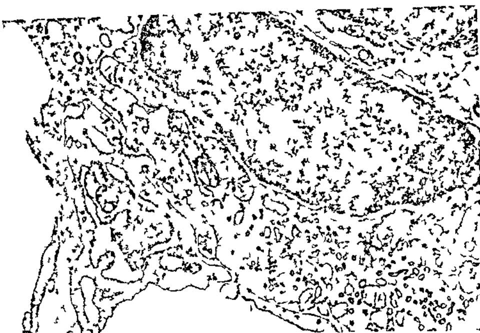


Fig 7 Group 0 Reticular cells with scanty electron dense material in the nucleus scant endoplasmic reticulum and few aggregations of free ribosomes × 24 000

changed In some of the cells from the central parts of the group 8 tumours however the number of mitochondria was markedly decreased

The nuclei of tumour cells were often lobulated and contained electron dense material with over all spread in the nucleus (Figs 5 and 6) while the normal reticular cells had scanty dense material concentrated along the nuclear membrane (Fig 7)

The abundance of endoplasmic reticulum seems to vary considerably in different kinds of tumour cells In many carcinomas investigated the ergastoplasm has been found to be scanty and the majority of the ribosomes are free In other types of tumours — Rous sarcomas osteosarcomas myelomas and pituitary adenomas — the amount of ergastoplasm has been reported to be increased in comparison with the corresponding normal cells (EPSTEIN 1957 PEACH et coll 1961) It is obvious that the cells with abundant ergastoplasm of the rough type have a very high UV extinction and it is possible that they are responsible for the formation of collagen *which is* present in large amounts in these tumours Further investigations are in progress to elaborate on this point



Fig 6 Group 5 Tumour cell with numerous mitochondria and sac like distension of endoplasmic reticulum (arrow) × 12 000

tumours, and in some of the tumour cells the endoplasmic reticulum was dense and almost exclusively of the rough type (Fig 5) In other cells it was scanty, and the ribosomes were mostly free Small aggregations of ribosomes were found in reticular cells of group 0 and 2 but they were larger and more numerous in cells of established tumours, especially in those with a scanty endoplasmic reticulum In some of the group 8 tumour cells there were few free and bound ribosomes, in these cells, other cytoplasmic organelles were also poorly developed, and they seemed to correspond to the centrally situated cells with low UV extinction values The endoplasmic reticulum of tumour cells characteristically had sac like distensions filled with electron dense material (Fig 6) Such distensions have been described in strontium induced fibroblastic osteosarcomas and other tumours (NILSSON 1962) but also in non tumourous inflammatory tissue (PEACH et coll 1961), and it has been demonstrated by GOLDBERG & GREEN (1964) that they are the site for collagen formation

The size and shape of the mitochondria were irregular both in tumourous and non tumourous reticular cells but the internal mitocondrial architecture was un

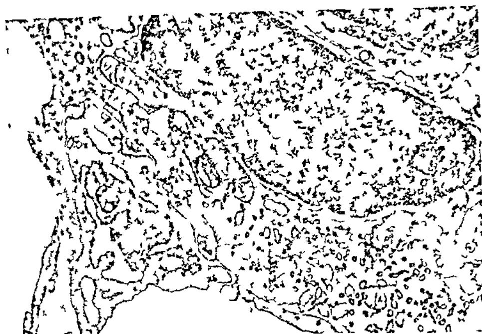


Fig 7 Group 0 Reticular cells with scanty electron dense material in the nucleus scanty endoplasmic reticulum and few aggregation of free ribosomes × 24 000

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SUMMARY

^{90}Sr induced osteosarcomas in different stages of development were investigated by means of ultraviolet microphotometry and electron microscopy Successively increasing UV extinction values could be correlated to morphologically more advanced stages of tumour development

ZUSAMMENFASSUNG

Osteosarkome in verschiedenen Entwicklungsstadien, die durch Strontium 90 verursacht waren wurden mittels der ultravioletten Mikrophotometrie und Elektronenmikroskopie untersucht Successiv zunehmende UV Auslöschungswerte konnten mit morphologisch fortgeschrittenen Stadien der Tumorentwicklung korreliert werden

RÉSUMÉ

Des ostéosarcomes induits par le ^{90}Sr à différents stades de développement ont été examinés par microphotométrie en ultra violet et par microscopie électronique On a pu établir une corrélation entre les valeurs croissantes d'extinction du cytoplasme en ultra violet et les stades d'avancement morphologique du développement des tumeurs

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FROM THE RADIUM CENTRE FOR JUTLAND (PROF S KAAE) AARHUS DENMARK

TOPICAL TREATMENT OF ULCERATIVE MAMMARY CARCINOMA BY THIOTEPA COMPRESSES

by

A P ANDERSEN H BRINCKER and A SELL

The alkylating cytostatic thiotepa (N N N triethylene thiophosphoramide) has been used since 1953 for the palliative treatment of a large number of malignant diseases It has usually been administered parenterally but topical application has also been tried successfully in certain benign and malignant conditions The intrapleural and intraperitoneal instillation of thiotepa performed once to several times in single doses of 10 to 65 mg has proved effective in the treatment of recurrent malignant effusions BATEMAN et coll (1955) for instance reported good effects in eleven out of sixteen patients with pleural effusion and in five out of eight patients with peritoneal effusion GROESBECK & CUDMORE (1962) found the same favourable effect in thirteen out of fifteen patients with pleural effusion and in seven out of twelve with peritoneal effusion

A number of widespread benign and malignant bladder papillomas have been sucessfully treated by intravesical instillations of thiotepa The doses have generally been 30 to 60 mg repeated four to six times at intervals of 2 to 7 days The effect has been most marked upon superficial papillomatous tumours while infiltrating tumours have failed to respond JONES (1963) for

Submitted for publication 11 December 1967

SUMMARY

^{90}Sr induced osteosarcomas in different stages of development were investigated by means of ultraviolet microphotometry and electron microscopy Successively increasing UV extinction values *could be correlated to morphologically* more advanced stages of tumour development

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Osteosarkome in verschiedenen Entwicklungsstadien die durch Strontium 90 verursacht waren wurden mittels der ultravioletten Mikrophotometrie und Elektronenmikroskopie untersucht Successiv zunehmende UV Auslöschungswerte konnten mit morphologisch fortgeschrittenen Stadien der Tumorentwicklung korreliert werden

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Table

Results of treatment with thiotepa in 11 patients with ulcerating breast cancer during the period October 1964 to August 1966

Case	Age	Lesion	Applications/days	Total dose thiotepa mg	Additional treatment
1	64	Adenocarcinoma	25/33	375 mg	Prednisone
2	63	Carcinoma	15/?	225 mg	Stilboestrol + prednisone
3	56	Sol. scirrh. carcinoma	23/23	345 mg	Hypophysectomy 9 months/earlier
4	72	Sol. carcinoma	28/28	420 mg	None
5	47	Intracanal carcinoma	19/19	285 mg	Prednisone
6	59	Scirrh. carcinoma	13/13	185 mg	Testosterone
7	75	Sol. scirrh. carcinoma	21/21	915 mg	Prednisone
8	56	Carcinoma	22/40	330 mg	Prednisone
9	64	Scirrh. carcinoma	12/19	180 mg	Prednisone
10	61	Carcinoma	82/12?	1 230 mg	Stilboestrol
11	51	Sol. scirrh. carcinoma	14/16	210 mg	Prednisone

* Symbols: — no effect; + sporadic epithelialization; + + 50 per cent epithelialization; + + + total epithelialization.

instance, reported total or almost total disappearance of multiple papillomatous tumours in seventeen out of twenty four patients. Esquivel et coll. (1965) recorded complete tumour destruction in three, and partial destruction in two out of eight patients with benign papillomatosis. Two of a group of twelve patients with carcinomatous lesions responded only slightly; the tumours were quite superficial (stage A) *in both. In all the other patients with more* deeply infiltrating tumours the treatment was ineffective.

Cheng & Veenema (1965) applied thiotepa topically in six patients with

Table *(cont)*

M n alues/μl Leucocytes (L) Platelets (P)	Effect	Survival after treatment months	Comments
No d pres ion	+++	6	(See Fig 1)
No haem tolog c cont ol	+++	13	(See Fig 2)
No depress on	++	9	Recurrent ulceration 6 months later New top cal th otepa without effect
No d press on	++	4	
L 2100 P no depres ion	++	1 /	Add t onal intrapleural thiotepa (45 mg)
No dep es ion	++	2	
L 100 P 10 000	+		(See F g 3)
No depress on	+	14	
No d pres ion	—	8	
L 1100 P 12 000	++	8	Ulcerating pr mary tumour
No dep ess on	+	5	Pyocya eus infect on du ng thiotepa treatment

penile tumours In dealing with tumours of the urethra they used suppositories of 15 mg applied once daily for 2 hours while tumours affecting the glans penis were bathed in a solution of 60 mg thiotepa in 60 ml distilled water once or twice daily for 2 hours at a time Out of four patients with condylomata acuminata they obtained complete disappearacne of the lesion in one patient in whom the lesion affected the urethra and partial disappearance in three patients in whom the lesions affected the glans Superficial regression of the tumours was achieved in only two patients with squamous cell carcinoma

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5	47	Intracanal carcinoma	19/19	285 mg	Prednisone
6	59	Scirrh. carcinoma	13/13	185 mg	Testosterone
7	75	Sol. scirrh. carcinoma	21/21	945 mg	Prednisone
8	56	Carcinoma	22/40	330 mg	Prednisone
9	64	Scirrh. carcinoma	12/19	180 mg	Prednisone
10	61	Carcinoma	8[illegible]/122	1 230 mg	Stilboestrol
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Fig 1 Case 1 a) Ulceration in the metastatic scar b) Total epithelialization 33 days later after 25 applications of thiotepa

ulcerated area while in five patients the epithelialization covered more than 50 % of the area Three patients had scattered epithelialization while the treatment failed in one patient who will be discussed later

Illustrative cases

Case I Woman aged 64 underwent right side mastectomy with axillary dissection in March 1961 The microscopic examination disclosed adenocarcinoma Postoperative irradiation by the McWhirther field technique was given

Progressive cutaneous metastases around the mastectomy scar were present in November 1963 In March 1964 there were diffuse neoplastic infiltrations in the entire left breast and left side axillary metastases simple palliative left mastectomy was then performed and in April treatment with androgenic hormones was started The skin metastases regressed slightly In September 1964 carcinosis of the right pleural cavity was treated by pleural puncture and instillation of ^{198}Au

Progression of the cutaneous metastases was noted in February 1965 and an area of ulceration 5 cm × 7 cm appeared in the right mastectomy scar (Fig 1a) The androgenic therapy was discontinued and prednisone was instituted At the same time the ulceration was treated with thiotepa compresses (25 applications/33 days with a total of 375 mg thiotepa) This resulted in total epithelialization of the area (Fig 1b) while other non ulcerating cutaneous lesions progressed

In September 1965 there were signs of hepatic metastases and death occurred at the end of the month

A few patients with *mycosis fungoides* have been treated by *thiotepa 0.2 %* in a lanolin petroleum jelly base and were much improved (GRUPPER & SIRKIS 1965, MICHEL et coll. 1965).

The recurrence rate of pterygium, reported to be 20 % to 30 % after surgery alone, may be greatly reduced by the postoperative instillation into the conjunctiva of thiotepa 0.05 % in Ringer's solution every third hour for 6 to 8 weeks. This treatment is said to produce no local irritation. CASSADY (1966) has reported the results of treating 78 patients, among whom there were six recurrences; out of this series, however, forty six had been treated for more than 2 months and in these there were no recurrences.

VOUTILAINEN & SALMI (1965) have published two cases of ulcerating cutaneous metastases from mammary carcinoma treated with compresses soaked in thiotepa solution. In one of these cases they used a solution of 15 mg thiotepa applied once daily, with a total of 20 applications in the course of 36 days. Colimycin compresses were used in the intervals between the applications. Three months after the discontinuation of the treatment the ulceration had undergone epithelialization. In the other case, they employed a solution of 30 mg thiotepa, applied 8 times in the course of 21 days. One month after the treatment had been discontinued the ulceration had diminished but thereafter it again progressed.

We have tested the last mentioned method, which is easy to administer and has produced good palliation in several cases.

Method. An amount of 15 mg thiotepa is dissolved in 20 to 30 ml sterile water. A compress of the same size as the ulceration is soaked in the solution, applied to the ulcerated site, covered with gutta percha, and held by an ordinary dressing. The compresses are changed daily. While the treatment is continued, white cell and platelet counts are made 2 to 3 times weekly. Should signs of bone marrow depression appear, the applications should be interrupted immediately and not be resumed until the marrow has been restored to normal.

Results

We have treated 11 patients with ulcerating breast cancer by the above procedure during the period October 1964 to August 1966. The results are given in the Table.

One patient (Case 10) had an ulcerating primary tumour, while the others had cutaneous metastases that had ulcerated. The material was *not selected*, except for the fact that only patients in an acceptable general condition were included. In two patients, the treatment resulted in total epithelialization of the



Fig 3 Case 7 Widespread ulceration of the metastatic areas on the anterior aspect of the right chest and right upper arm

given but again had no effect upon the necrosis Electron therapy (10 MeV 3 150 rad/31 days) also seemed ineffective Distant metastases gradually appeared and the patient died in November 1966

Discussion

Alkylating agents are chemically very active substances whose cytotoxic effect presumably consists mainly in an inhibition of the DNA synthesis Morphologically the effect is apparent as an inhibition of mitotic activity with characteristic chromosomal breakages The cytotoxic action is not selective and therefore the concentration in the tumour should preferably be higher than in the surrounding tissue This is obtained by topical application of the agent

The treatment with thiotepa compresses failed entirely in one of the patients in the present series (Case 9) The characteristics of this case was ulceration covered with thick encrustations, which is *possibly* the explanation of the absence of any effect from the thiotepa

Ten of the eleven patients received hormone medication at the same time as the thiotepa application The cases were analysed with a view to assessing to what extent the hormone may have contributed to the effect In two instances (Cases 1 and 10) the hormone medication was started almost simultaneously with the thiotepa applications which makes the evaluation difficult but in these two cases other metastatic lesions progressed in spite of



Fig. 2. Case 2. a) Ulceration of widespread cutaneous metastases. b) Total epithelialization after 15 applications of thiotepa.

Case 7. Woman, aged 75, had right side mastectomy in March 1963. Microscopy showed scirrhous carcinoma. No postoperative radiotherapy.

In September 1964 *increasing number of cutaneous metastases in the right chest* and right upper arm; prednisone medication was ineffective.

In February 1965 there was also widespread ulceration in the metastatic areas on the anterior aspect of the right chest and right upper arm (Fig. 3). Treatment with thiotepa compresses was instituted (21 applications/21 days with a total of 945 mg thiotepa). Epithelialization began to appear along the margins and central islets of epithelium were observed, but at the same time the absorption of thiotepa from the ulcerated surfaces severely depressed the bone marrow. There was a fall in the white blood count to 100/μl and of the platelets to 10 000/μl. In spite of prednisone in large doses the bone marrow could not be restored and the patient died of profuse rectal bleeding due to severe thrombocytopenia a month later.

Case 9. Woman, aged 64, who in February 1962 had ulcerating carcinoma of the left breast. Preoperative radiotherapy was followed by right mastectomy in April 1962. Microscopy *showed diffuse scirrhous carcinoma.* Postoperative irradiation of the regional lymph nodes and roentgen castration.

In November 1964 there were cutaneous metastases on the anterior surface of the right chest, with ulceration 2 cm × 2 cm in size which yielded to local irradiation.

In August 1965 further progression of lesion with ulceration despite prednisone therapy. The lesion measured 12 cm × 18 cm in February 1966; there was a 7 cm × 7 cm large central area of ulceration and marked necrosis. Treatment with thiotepa compresses was started (12 applications/19 days with a total of 180 mg thiotepa). The treatment had no effect either upon the ulcerations or upon the necrosis. *Prolonged energetic antiseptic therapy topically* was



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therapy, or who were simultaneously on parenteral chemotherapy CHENG & VEENEMA observed a slight depression of the white blood count in the topical treatment of penile and urethral tumours with thiotepa MICHEL et coll have reported a case of leukocyte and platelet depression after the topical treatment of mycosis fungoides with a total dose of 1 4 g thiotepa/34 days CASSADY noted no absorptive side effects in the treatment of pterygium and VOUTILAINEN & SALMI observed no such effects in their two patients treated for ulcerative mammary carcinoma The present results indicate however that the blood picture should be carefully checked during the treatment which should be interrupted immediately if signs of bone marrow depression appear Furthermore it seems inadvisable to administer more than 15 mg thiotepa daily, and particular caution should be observed with large areas of ulceration and prolonged treatment

It does not seem reasonable to try this treatment unless the patients are in a fair general condition and are likely to survive for a certain length of time Incidentally the treatment is well suited for out patient use provided that the haematologic condition can be followed

SUMMARY

The results of the local application of thiotepa compresses to ulcerative mammary carcinoma in 11 patients are reported The risk of haematologic complications is stressed The literature on this topical treatment is reviewed

ZUSAMMENFASSUNG

Es wird uber die Resultate der Behandlung mit lokalen Kompressen von Thiotepa von 11 Patienten mit ulcerativen Mammakarzinomen berichtet Das Risiko von hamatologischen Komplikationen wird betont Die Literatur wird besprochen

RÉSUMÉ

Les auteurs présentent les résultats de l application locale de compresses imbibées de Thiotepa sur des cancers du sein ulcérés chez 11 malades Ils insistent sur le danger des complications hématologiques Ils donnent une revue de la littérature sur ce traitement local

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the hormone. In the other eight patients the medication had been instituted several months before the thiotepa treatment without having favourably affected the ulcerating area, so that it is not likely that the hormone had any share in the effect.

VOUTILAINEN & SALMI recommend the use of colimycin compresses during the intervals between the thiotepa applications in order to prevent the growth of microorganisms in the treated area. This or similar procedures were not used in the present series. One of the patients (Case 11) developed a pyocyaneus infection in the ulcerated area, while the others exhibited regression of superficial infectious lesions, in keeping with the fact that alkylating agents per se are bactericidal.

Three of the patients developed signs of bone marrow depression in the course of the treatment. This manifested itself as a decrease in the white cell or platelet count. In one of these patients (Case 5), however, it was difficult to assess the share in these complications of the thiotepa compresses as, due to a pleural effusion, intrapleural thiotepa therapy (45 mg) was administered at the same time. Case 10 developed a depression of the bone marrow after prolonged treatment (1 230 mg thiotepa/122 days) in spite of a rather small area of ulceration (about 13 square cm), the signs consisted of decreased white cell and platelet counts and progressing anaemia. In the course of a month blood transfusions restored the haematologic condition to normal, however. Case 7 had very widespread ulcerating lesions and was given a daily dose of 15 mg thiotepa (the usual is 15 mg). In the course of three weeks there was a massive decrease in the haemoglobin level, white cell and platelet counts, and the patient died of haemorrhagic diathesis.

Thiotepa, whose molecular weight is 189, can be absorbed to a certain extent from the outer and inner surfaces of the body, especially if these have undergone pathologic changes. Indeed, others have also reported absorptive side effects with thiotepa. ESQUIVEL et coll., for instance, observed an action upon the bone marrow in five out of twenty patients treated by intravesical instillations of thiotepa, however, all rapidly improved. ORAVISTO (1965), treating six patients by intravesical thiotepa, found severe leukocyto- and thrombocytopenia after a total dose of 150 mg thiotepa in one patient while another patient died of massive hepatic necrosis 16 days after 120 mg thiotepa/7 days, after having had but a modest decrease in the white cell and platelet counts. EDGREN et coll. (1966) have also published a case of severe bone marrow depression after 360 mg thiotepa/8 days in the urinary bladder.

GROESBECK & CUDMORE found a slight haematologic depression in a few patients treated with thiotepa, administered intrapleurally and intraperitoneally, although only in those who had already received radiotherapy. Au-

therapy or who were simultaneously on parenteral chemotherapy CHENG & VEENEMA observed a slight depression of the white blood count in the topical treatment of penile and urethral tumours with thiotepa MICHEL et coll have reported a case of leukocyte and platelet depression after the topical treatment of mycosis fungoides with a total dose of 1 4 g thiotepa/34 days CASSADY noted no absorptive side effects in the treatment of pterygium and VOUTILAINEN & SALMI observed no such effects in their two patients treated for ulcerative mammary carcinoma The present results indicate however that the blood picture should be carefully checked during the treatment which should be interrupted immediately if signs of bone marrow depression appear Furthermore it seems inadvisable to administer more than 15 mg thiotepa daily and particular caution should be observed with large areas of ulceration and prolonged treatment

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FROM THE DEPARTMENT OF GYNAECOLOGY (DIRECTOR P KOLSTAD), THE NORWEGIAN RADIUM HOSPITAL OSLO NORWAY

TREATMENT METHOD AND DOSE DISTRIBUTION IN RADIOTHERAPY OF CARCINOMA OF THE CERVIX

by

PER BERGSJO and PER KRISTIANSEN

The basic principles of radiation treatment of carcinoma of the uterine cervix in our hospital have remained unchanged since 1932 With the exception of a report by GRANDE (1958) on the dosimetry of a special vaginal applicator no detailed account of the system seem however to have been published Our aim with the present paper is to present the whole procedure including the dose distribution as it has been practised up to now The system will be referred to as the Oslo method

Principles and techniques of the Oslo method Radium is the standard primary treatment of all forms and stages of invasive cervical carcinoma It is exhibited either as the only form of treatment or supplemented by surgery (early stages) or external radiation (more advanced stages) Detailed accounts of the various combinations of surgery and irradiation in early stages have been given by SCHJOTT RIVERS (1951) DAHLE (1959) and KOLLER (1964) and the interested reader is referred to these reports

The radium treatment is a modification of the Paris method and consists of two applications one intra uterine and one intravaginal The intra uterine

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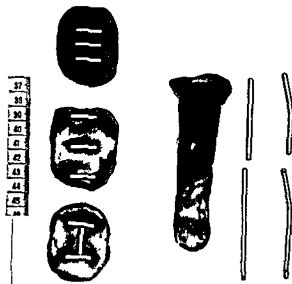


Fig 1 Intrauterine and vaginal applicators A vaginal applicator is seen in the middle The three configurations of vaginal radium are referred to as (from top to bottom) I II *and III in the text*

applicator carries 20 or 30 mg radium, depending on the length of the uterine cavity, and the intravaginal applicator bears 30 mg radium The duration of each application is 120 hours (5 days) to produce a total of 6 000 or 7 200 mg hours of radium As the two applicators may be employed either simultaneously or in succession, the same total dose may be given at two different dose rates

The intra uterine applicators (Fig 1) are straight or slightly angulated cylinders, measuring 6 mm × 80 mm (active length 68 mm) and 6 mm × 58 mm (active length 44 mm) for 30 and 20 mg radium, respectively The filter equals 1 5 mm Pt

The vaginal radium is applied in 10 mg tubes of gold or platinum, with an active length of 13 5 mm, and a filter equal to 1 mm Pt The three vaginal tubes are usually placed on the shallow, bell shaped end of an applicator moulded by hand to fit the individual cervix and tumour from a dental impression compound (Kerr s paste) The tubes are placed sagittally or in an H form, with 20 to 40 mm separating the lateral tubes Also a pessary shaped plastic applicator without shaft (GRANDE 1958) which is used in individual cases has the shape of an H Three different configurations of vaginal radium applicators are given in Fig 1

The external radiation was previous to 1958 administered with 170 kV roentgen rays (filter 1 mm Cu), 3 000 R at the skin, to two anterior and two posterior fields, each 10 cm × 15 cm in size, delivered over approximately 40 days

Betatron treatment has been the rule since 1958 All the patients received 31 MeV roentgen rays from a betatron until 1964 but since then a number of

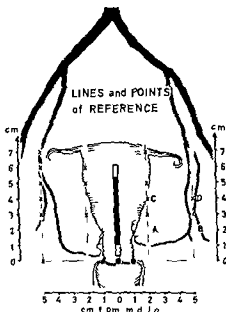


Fig 2 Lines and points of reference Of the three vaginal tubes r_1 lies closest to and r_3 farthest away from the side of reference

patients have been treated with 33 MeV roentgen rays from a new betatron the old betatron was utilized for the remainder

The 31 MeV machine has a circular pelvic field 20 cm in diameter (total 314 cm), and each daily fraction is 200 rad The total dose of a standard treatment for carcinoma of the cervix was 4 000 rad from 1958 to 1960 since then it has been 5 000 rad to the periphery (pelvic wall area) the central dose being kept at 4 000 rad with a central shield 7 cm in diameter These doses refer to the absorption maximum located about 5 cm below the body surface Half of the treatments are given from the front and half from the back

The 33 MeV machine has a 16 cm × 16 cm (256 cm) pelvic field A shield in the lower central part of the field was designed to produce doses equal to those of the 31 MeV apparatus The daily fractions and total doses are as described above

The daily fractions are given 5 to 6 times per week An uninterrupted series of betatron treatment is spread over four to five weeks

Measurement of dose distribution Some simple measurements have been performed in a special phantom to obtain knowledge of the dose distributions and an idea of the doses absorbed at certain points The further aim of these measurements was to check the reliability of the calculated values which are based on

standard tables and isodose charts Rectal dose measurements in a series of patients with radium applications have also been made

Points of reference The *anatomical points of interest are the tumour itself, the* parametrium, and the lymphatic system The rectal dose is of major importance regarding side effects Based on these considerations certain lines and points of reference were defined, and a phantom was constructed according to these principles

The points of reference lie along *two straight lines parallel to the uterine* canal 2 cm and 5 cm, respectively, lateral to it in the sagittal planes, for the sake of simplicity the uterine canal is considered as a straight line The medially situated line corresponds to the median part of the parametrium, which is the tumour bearing area in cervix carcinoma stage II B The lateral line is in the area of the pelvic wall, as shown in Fig 2

The commonly adopted points of reference, points A and B, are located on the lines of reference As defined by TOD & MEREDITH (1953), point A lies 2 cm lateral to the central canal of the uterus and 2 cm above the mucous membrane of the lateral fornix in the axis of the uterus, point B lies 3 cm lateral to point A at the same level In addition to points A and B the doses at two other points, called C and D, have been calculated, these are located 2 cm above the former points on the median and lateral lines of reference, respectively, as shown in Fig 2

An accurate determination of the betatron contribution on the lines of reference is difficult because of individual variations Considering that the treatments are generally given both from the front and the back, the 10 cm depth dose was thought to represent the average dose in the target area The frontal plane 10 cm from the body surface was therefore chosen for reference

Measurement of radium doses As previously explained the vaginal radium tubes are placed on the applicators to cover the individual tumour in the best possible way, which of course means individual differences in dose distribution We have *studied the doses delivered by the three different configurations* I II and III illustrated in Fig 1 These are typical forms used to treat a wide range of cervical carcinomas of all forms and stages

A perspex phantom (Fig 3) was designed to accommodate the three vaginal radium tubes of configuration I and the straight uterine applicators The design permitted several angles (30°, 60°, 90°, and 120°) between the planes of the vaginal tubes and the uterine canal following the anatomical variations from anteversion to retroversion Holes for dose measurements are situated along the defined lines of reference, with a special *hole for rectal measurements which lies*



Fig 3 The perspex phantom (For explanation see text)

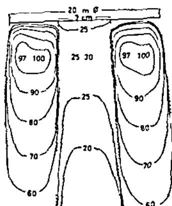


Fig 4 Isodoses of the 31 MeV betatron central shilding Roentgen rays FSD 100 cm

at a minimum of 3 cm from the point of the external os The doses were measured with a Siemens gammameter The maximum rectal dose has also been determined with the same Siemens gammameter in a series of 231 consecutive patients with carcinoma of the cervix stage II during the vaginal radium insertion

The radium doses were also calculated with the help of MEREDITH's (1949) tables A slight approximation was allowed in the positioning of the intra uterine radium to simplify the calculations but otherwise the conditions matched those of the phantom

Accuracy of the measurement Perspex which was used for the phantom is not quite equivalent to tissue as regards dosimetry However as the present problem concerned doses for clinical purposes perspex seemed satisfactory although polystyrene might have been a better choice of material

At short distances the relatively small differences in density between perspex and tissue are negligible and even up to 8 cm the heavier absorption in perspex will mostly be counteracted by a higher rate of scattered radiation With the purposes we had in view we might have measured in free air but a phantom appeared better for achieving the given configurations

The phantom measurements were checked for reliability in two ways First by comparing the values obtained from two separate insertions with those from a simultaneous insertion of vaginal and uterine radium The former happened to exceed the latter by an average of 9 per cent in the area 0 to 2 cm from the level of the external os and by about 4 per cent at the points farther way from the tumour area As the simultaneous measurements agreed best with the calculated

Table 1

Individual and total doses (in rad) from vaginal radium tubes for the different configurations (see Fig 1) values calculated at points A B C and D The numbering of the radium tubes is explained in Fig 2

	Configuration I				Configuration II				Configuration III			
Points	A	B	C	D	A	B	C	D	A	B	C	D
r_1	1 670	410	490	260	2 030	640	520	330	1 670	410	490	260
r_2	1 040	290	440	200	1 040	290	440	200	900	90	340	60
r_3	670	200	330	160	400	160	260	130	670	200	330	160
Total	3 380	900	1 260	620	3 470	1 090	1 220	660	3 240	700	1 160	480

values, and as the separate measurements must be used for special comparisons, both sets of values were utilized in the results Secondly, the phantom measurements were tested for reliability by comparing the measured values with the calculated ones These were in close agreement, with differences from 1 to 5 per cent in both directions

A comparison of the clinical and phantom rectal doses is given under 'Results

Determination of betatron doses The isodose charts of the two betatrons were used to find the 10 cm depth contribution in the lines of reference The 31 MeV *isodoses with the central shields are given in Fig 4 The isodoses from the* 33 MeV betatron (not shown) were similar Isodose charts without central shielding were also consulted since part of the treatment was unshielded

For purposes of comparison, the RBE *of the roentgen rays from the* betatrons may be set arbitrarily as equal to 0 8 This value lies within the range found by OFTEDAL (1956) and by MOSSIGE (1956), who tested our betatrons, and that reported by KOHN (1958)

Results

Contribution by radium The doses delivered by the three different vaginal applicators including the contribution by the individual radium tubes, are presented *in* Table 1 It is evident that with the tubes in the H form (configuration III), the doses at all four points of reference are reduced in comparison to those given by three parallel tubes (configurations I and II) The reduction is considerable at the points corresponding to the pelvic wall (B and D) Configurations I and II produce almost equal doses at all points except point B corresponding *to the obturator region, where the latter is obviously most effective*

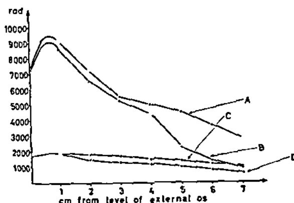


Fig 5 Combined contribution of uterine and vaginal applicators at the respective lines of reference
A — uterine 30 mg vaginal 30 mg 2 cm from uterine cavity
B — uterine 20 mg vaginal 30 mg 2 cm from uterine cavity
C — uterine 30 mg vaginal 30 mg 5 cm from uterine cavity
D — uterine 20 mg vaginal 30 mg 5 cm from uterine cavity

Turning to the relative contribution by the individual tubes the highest difference between tubes r_1 and r_3 lies at point A the difference being less marked at the three points farther away from the tumour area

The individual contributions of the two uterine applicators are shown in Table 2 The doses from vaginal and uterine applications combined are given graphically in Fig 5 With 20 mg of radium instead of 30 mg in the uterine cavity there is a considerable difference in the dose at the median line of reference more than 4 cm away from the fornix This corresponds to the upper part of the uterine surface which is relatively unimportant therapeutically The total contribution does not exceed 2000 rad along the pelvic wall line and the difference between the two combinations is below 500 rad at all the points The rapid fall in dose between the median and lateral lines at the 0 to 3 cm levels is also worth noting as this corresponds to the common area of tumour spread

In Table 3 the relative individual contributions of the vaginal and uterine applications are recorded Both contribute about equally to the total dose at point A The vaginal contribution along the pelvic wall varies from 64 per cent in the obturator region to 50 per cent in the iliac region when the uterus contains 20 mg radium With 30 mg radium in the uterus the relative vaginal contribution is slightly lower but it does not fall below 40 per cent of the total dose in the area measured

The doses measured in the phantom in the ante and retroverted uterine positions were little different from those in the median position The rectal doses were however higher with a retroverted uterus Considering the true anatomy in which the positioning of the uterus does not influence the conditions of the pelvic wall it is likely that intra uterine radium in the anteverted position will produce a higher relative contribution to the common and external iliac areas

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Total	3 380	900	1 260	620	3 470	1 090	1 220	660	3 240	700	1 160	480

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Table 5

Contribution of vaginal radium (in per cent) to total maximum rectal dose (in rad) at separate insertions with 30 mg vaginal and 30 mg uterine radium

	Rad	Per cent
Anteversion	2 950/4 300	69
Median position	2 950/4 550	65
Retroversion	2 950/4 800	61

The 31 and 33 MeV betatrons produced almost equal results in the plane of reference the difference being less than 100 rad at 75 per cent of the points and nowhere exceeding 300 rad The dose distribution is also fairly homogeneous being about 3 500 rad along the pelvic wall, and about 3 000 rad in the median line of reference

As mentioned previously, the betatron doses to the periphery were raised in 1960 The pelvic wall doses should be reduced by 20 per cent to correct for patients treated between 1958 and 1960 (with the 31 MeV machine only)

Fig 6 giving betatron isodoses in two patients of different body size are presented both to illustrate the dose distribution in anatomical sections and to demonstrate individual differences

Discussion

Radiation treatment has developed from an empirical art to a science of dosimetry the aim now being to eradicate the primary tumour and destroy possible pelvic metastases while protecting vital structures from radiation injury The ways to achieve this differ slightly among the various treatment systems

In the Manchester system the need for individual dosimetry is stressed According to TOD & MEREDITH (1953) the optimum dose to point A from radium is 8 000 rad delivered in two three day sessions (total 144 hours) but only 6 500 rad if the patient is over 65 years old or if supplementary roentgen rays are given KOTTMEIER (1954) has stated that in the Stockholm method the radium contribution to point A does not exceed 6 500 rad delivered in 50 to 60 hours In the Oslo system described in this paper the point A dose varies from 6 500 to 7 200 rad delivered in 120 to 240 hours The rule in recent years has been 240 hours that is two separate insertions The dose rates must be taken into account in comparing the effect of the different systems

Table 2

Individual contribution (in rad) from the two types of uterine applicators at different points

Active length	Points A	B	C	D
44 mm	3 150	630	3 150	630
68 mm	3 790	880	3 790	880

Table 3

Relative individual contributions (in per cent) from vaginal and uterine applicators The values indicate the vaginal dose as a percentage of the total Vaginal configuration I is combined with both types of uterine applicators

		Vaginal 30 mg uterine 20 mg		Vaginal 30 mg uterine 30 mg	
Distances from uterine axis		5 cm	2 cm	2 cm	5 cm
Distance from plane of fornix	6 cm	50	47	21	40
	5 cm	53	31	21	42
	4 cm	50	29	26	41
	3 cm	54	34	33	49
	2 cm	57	52	47	51
	1 cm	64	67	66	58

Table 4

Maximal rectal doses (in rad) with simultaneous insertions in different uterine positions

	Vaginal 30 mg uterine 20 mg	Vaginal 30 mg uterine 30 mg
Anteversion	3 150	Not measured
Median position	3 450	3 800
Retroversion	3 700	4 000

The rectal doses measured in the phantom are the least reliable from the anatomical point of view The results are recorded in Tables 4 and 5 The maximum rectal doses in 231 patients with cervical carcinoma stage II during vaginal radium insertion were 2 550 rad ± 700 rad (mean and standard deviation) this agrees well with the phantom dose of 2 950 rad

Contribution by external radiation The estimated dose at the mid pelvis was 2 000 rad/40 days with 170 kV roentgen rays as used prior to 1958

do e It must also be remembered that the point of the maximum dose in the rectum may be different in the uterine and vaginal applications, which again reduces the risk of rectal damage Experience also suggests that the rate of com plications in the Oslo system is reasonably low and that it appears to be dose rate dependent (BERGSJO & EVANS 1964)

Regarding external treatment both KOTTMEIER (1963) and TOD & MEREDITH (1953) agree that the dose to the parametrium should be 3 000 R/four weeks KOTTMEIER increases this dose to 5 000 R in advanced cases The betatron con tribution to the parametrium in the Oslo system is about 3 500 rad but a direct comparison is difficult to make because of the uncertainty of the relative biologic effectiveness

Without going into details we should like to point out that the Oslo system is well tolerated although the patients are confined to bed for two periods of five days Complications requiring interruption of the radium insertions are exceptional With regard to radiation hygiene the operators and technical staff handling the radium during the actual insertions receive smaller doses in the Oslo system from each application than from the larger amounts of radium used in the other systems Although members of the nursing staff come into contact with the pa tients several times a day constant dosimetry has revealed that they and the per sonnel in charge of the radium applications are kept well below the permissible tolerance limits of radiation (GRANDE & JAHREN 1965) From this point of view the ideal is an automatic loading system

Acknowledgement

This investigation was in part supported by a grant from the Alexander Malthe s legacy sponsored by Oslo Surgical Society The perspex phantom was made at the Norsk Hydro Institute for Cancer Research Dr Bergsjø was a fellow of the Norwegian Cancer Society during this investigation

SUMMARY

The Norwegian system of radiation treatment for carcinoma of the uterine cervix is described in detail The order of magnitude of the pelvic doses has been determined with the help of a perspex phantom standard calculation tables and clinical measurements The system is compared to the Manchester and Stockholm systems with special reference to the different dose rates of the radium applications

ZUSAMMENFASSUNG

Die norwegische Methode der Strahlentherapie des Uteruskarzinomes wird eingehend be chri ben Die Grös e der Beckendosen wurde m t Hilfe eines Perspexphantomes mittels Standardrechentabellen und klinischen Messungen ermittelt Das System wird mit den Manchester und Stockholm Systemen verglichen Besondere Beachtung wird den verschie denen Intensitaten der Radiumstrahlenkorper gewidmet

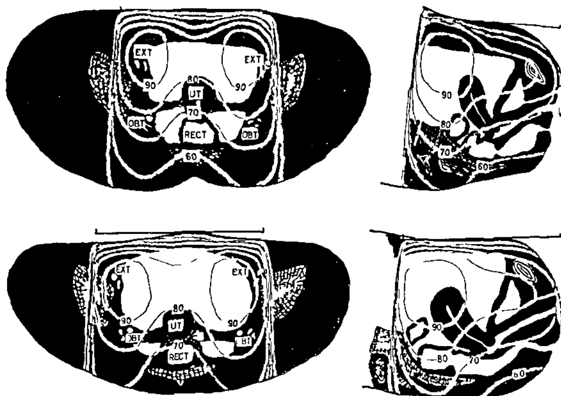


Fig 6 Isodoses from 33 MeV betatron roentgen rays pelvic fields 16 cm × 16 cm resulting from 200 R × 12 unshielded and 200 R × 13 with shielding of the lower central part of the field all treatments given from the front Cross and sagittal sections in two patients of different body size

ELLIS (1963) has shown that the doses producing the same effect with different times are connected by the relationship

$$\frac{D_1}{D_2} = \left(\frac{T_1}{T_2}\right)^{0\ 6}$$

With this formula, the dose range at point A according to the Oslo system is equivalent to 5 700 to 6 300 rad in the Manchester system and to 4 500 to 5 000 rad in the Stockholm system, indicating that the dose effect of the Oslo system with two separate radium insertions is probably slightly lower at point A as compared to the two former systems

KOTTMEIER (1963) paid much attention to the doses in the bladder and rectum and stated that these should not exceed 5 500 R and 4 000 R respectively (1 R = 0 97 rad) The rectal dose of the Oslo system lies between 4 300 and 4 800 rad/240 hours, which, with Ellis formula produces the same effect as 3 000 to 3 350 rad/60 hours, or considerably below the permissible maximum

SERVICE DE CURIETHERAPIE (PROF B PIERQUIN) ET SERVICE DE RADIO PHYSIQUE (MME A DUTREIX) INSTITUT GUSTAVE ROUSSY VILLEJUIF, FRANCE

ENDOCURIETHERAPY — A DOSIMETRIC STUDY OF TWO PARALLEL RADIOACTIVE SOURCES

by

B Pierquin A Dutreix C Paine D Chassagne and A Wambersie

The basic principles of our new method for endocurietherapy (this term refers to implants of radioactive isotopes into the tissues) were outlined in a recent article (Pierquin & Dutreix 1967) Although the final analysis of dosimetry is made from the actual distribution of the radioactive material in the patient it is necessary to develop a preliminary distribution plan to help the radiotherapist to plan the optimum arrangement in given circumstances Some basic information for the preliminary distribution plan is developed in the present paper and represents a systematic study of the dosimetry around two straight parallel radioactive sources of equal length Our work will subsequently be extended to cover the varying clinical and geometric conditions that can be foreseen and rules for the optimum distribution of the radioactive material will then be set up

Methods

The calculations were made by computer the dose being calculated at 1 500 points around the sources for each plane of interest and at the desired degree of magnification of the calculated plane with respect to the size of the source (Dutreix 1967) (Fig 1)

Submitted for publication 11 September 1967

RÉSUMÉ

Les auteurs decrivent en detail la methode norvegienne de traitement par les radiations du cancer du col de l uterus L ordre de grandeur des doses pelviennes a été determine sur un fantome en perspex avec des tables de calcul standard et par des mesures cliniques Cette methode est comparee aux methodes de Manchester et de Stockholm en particulier en ce qui concerne les doses differentes d application de radium

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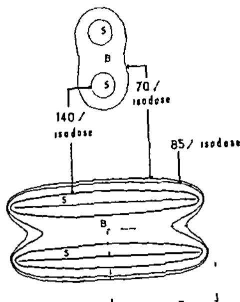


Fig 2 Reconstruction of the complete plane (cf fig 1) The 140 % isodose encloses the high dose zone corresponding to a reference isodose of 70 % The example taken is for 6 cm sources separated by 1 68 cm The basal dose (B) is 671 rad per 24 hours

separation = the separation of the sources has been taken to vary between 0 8 cm and 2 1 cm

The reasons for these choices of length and separation are discussed below

The terms for the treatment volume are defined as follows

basal dose = the maximum dose in the plane of the two sources midway between them and equidistant from their ends

reference isodose (RI) = the isodose corresponding to the envelope enclosing the treatment volume (we have studied two treatment volumes enclosed by reference isodoses whose values are 85 % and 70 % of the basal dose respectively RI 85 % and RI 70 %)

high dose zone = that zone of high dosage surrounding each source which is enclosed by the isodose whose value is twice that of the reference isodose (Fig 2)

length = the distance between the limits of the treatment volume in its axis parallel to equidistant from and in the same plane as the source

width = the distance between the limits of the treatment volume in that axis which lies in the same plane as the sources but perpendicular to them

thickness = the distance between the limits of the treatment volume in the plane perpendicular to the sources and equidistant from them which is situated midway between their ends (Fig 3)

Under the conditions actually studied of the active length and separation of

B

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671	670	667	663	655	645	631	611	584	547	496	431	356	283	222
679	678	676	671	664	653	639	619	592	555	504	437	359	284	223
705	704	701	697	689	679	665	645	618	580	527	455	371	289	224
752	751	748	743	736	726	712	692	665	626	567	490	391	298	227
827	826	823	818	811	801	787	767	739	699	638	546	424	310	230
944	943	940	936	928	918	904	884	856	815	748	637	476	326	234
1133	1132	1127	1125	1118	1107	1093	1074	1045	1002	930	791	551	346	238
1484	1463	1461	1456	1449	1439	1425	1405	1377	1332	1253	1076	681	[illegible]	242
2156	2155	2152	2148	2141	2131	2117	2098	2069	2024	1938	1712	921	[illegible]	244
9999	9999	9999	9999	9999	9999	9999	9999	9999	9999	9999	9999	9999	[illegible]	246
9999	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	243
9999	9999	9999	9999	9999	9999	9999	9999	9999	9999	9999	9999	9999	[illegible]	239
1961	1960	1958	1953	1947	1938	1925	1907	1881	1838	1756	1542	850	[illegible]	231
1336	1335	1332	1328	1322	1313	1301	1283	1258	1217	1144	979	624	[illegible]	222
1013	1013	1010	1006	1000	992	980	963	939	901	834	710	[illegible]	309	212
816	815	813	809	803	795	783	767	744	709	653	555	[illegible]	281	201
682	681	679	675	669	661	650	635	613	582	532	[illegible]	352	256	190
584	584	582	578	572	565	554	532	[illegible]	[illegible]	[illegible]	386	308	235	180
515	[illegible]	[illegible]	504	[illegible]	491	481	467	449	[illegible]	385	335	274	216	170
452	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	424	411	393	370	338	296	247	200	161
404	404	402	398	393	387	378	365	349	328	300	264	224	185	152
365	364	363	359	355	348	340	328	313	294	269	239	206	173	144
332	331	330	327	322	316	308	297	283	266	244	218	190	162	137
304	303	302	297	294	288	281	271	258	242	223	200	176	152	130
279	279	277	274	270	265	258	248	237	222	203	185	164	143	123
258	258	256	253	249	244	237	229	218	205	189	172	153	135	117
237	239	237	235	231	226	220	212	202	190	176	160	144	127	112
223	222	221	218	215	210	204	197	187	177	164	150	135	121	107
208	207	206	204	200	196	190	183	175	165	153	141	128	115	102
194	194	193	190	187	183	178	171	164	154	144	133	121	109	98
182	182	181	179	176	172	167	161	153	145	136	125	115	104	94
171	171	170	168	165	161	157	151	144	137	128	119	109	99	90

Fig 1 Example of calculation page showing the idososes in the plane of the sources As the isodoses are symmetrical it is sufficient to calculate that portion of the plane that is shown

The limits of the present study are related to our practical experience, principally in the treatment of cancer of the skin The work has been based on our current techniques, using iridium 192 wire, which is after loaded into thin plastic tubes or hollow hypodermic needles, as described elsewhere (PIERQUIN 1964)

We first recall the definitions of volumes used in radiotherapy

tumour volume = volume occupied by clinically apparent tumour,

target volume = tumour volume plus a margin of surrounding normal tissue into which the clinician feels that extension of tumour is possible,

treatment volume = that volume whose limits are those of the reference isodose,

irradiated volume = a volume including all the above, plus such surrounding normal tissue as lies within a volume enclosed by the isodose whose value is 50 % of the reference isodose

As to the terms used, these are defined as follows for the radioactive material

active length = the whole length of the wire used is radioactive, and the lengths studied have been at centimetre intervals from 1 to 10 cm,

Table 1

Treatment volumes having same length and width

Length or width (cm)	Separation of sources (cm)	
	RI 70 %	RI 85 %
2.0	1.1	1.2
2.5	1.3	1.5
3.0	1.6	1.8
3.5	1.9	

B *Relations between the width of the treatment volume and the radioactive material*

1 Separation Width of treatment volume/separation of sources = 1.75 at RI 85 % and 1.90 at RI 70 %

2 Active length The width of the treatment volume remains almost independent of the active length for the same separation of the sources

C *Relations between thickness of treatment volume and radioactive material*

1 Separation Thickness of treatment volume/separation of sources = 0.5 at RI 85 % and 0.85 at RI 70 %

2 Active length The thickness of the treatment volume increases slightly as the active length of the sources increases from 1 to 10 centimetres from 0.46 to 0.59 at the 85 % isodose and from 0.77 to 0.92 at the 70 % isodose)

Inter relations between the dimensions of the treatment volume

1 Width and thickness

From relations B 1 and C 1 above it is evident that width and thickness are linked within the limits studied thus width/thickness at RI 85 % = 3.5 and at RI 70 % = 2.3

There is some variation in these values as the active lengths vary from 1 to 10 centimetres from 3.9 to 3.0 at the 85 % isodose and from 2.5 to 2.1 at the 70 % isodose

2 Length and width

There is a useful relation between the length and the width of the treatment volume If the width of the treatment volume is small the isodoses are such that the width is numerically greater than the length implying that the sources may be more effectively placed perpendicular to the long axis of the treatment

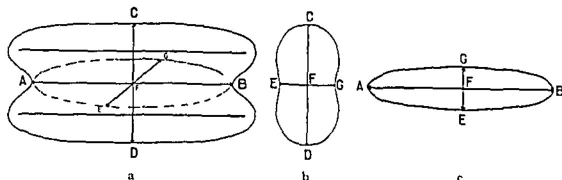


Fig 3 Dimensions of the treatment volume the figure being to scale for the 70 % isodose around 6 cm long sources separated by 1 68 cm a) Composite view showing the three dimensions length (AB) width (CD), thickness (FG), all taken through the central point (F), the position of the basal dose b) and c) show the two planes perpendicular to ABCD

sources, the dose rate calculated at the reference isodose varied between 750 and 1 500 rad per day when using iridium 192 wire of a linear activity between one and two millicuries per centimetre The total tumour dose at the reference isodose is generally taken as 7 500 rad for lesions treated solely by implants (PIERQUIN & DUTREIX 1967) This dose is delivered more rapidly for small volumes No correction is at present applied to attempt theoretical equivalence of biological effect to 7 day treatments The calculations have been made on the basis of placing the radioactive material in tissue (density = 1), a correction for attenuation in the tissues, according to measurements recently published (MEISBERGER & SHALEK 1965, MEREDITH, GREEN & KAWASHIMA 1966), has been applied

Relations between treatment volume and radioactive material

The dimensions of the treatment volume are simply related to the active length and separation of the sources Within the limits set, the length is determined only by the active length, and the width and thickness by the separation of the sources

A *Relations between length of treatment volume and sources*

1 *Active length* Length of treatment volume active length of sources = 0 7 at RI 85 % and 0 9 at RI 70 %

These values increase slightly as the active lengths increase from 1 to 10 centimetres, from 0 65 to 0 75 at the 85 % isodose and from 0 88 to 0 94 at the 70 % isodose

2 *Separation* The length of the treatment volume is virtually independent of the separation of the sources

Table 1

Treatment volumes having same length and width

Length or width (cm)	Separation of sources (cm)	
	RI 70	RI 85
2 0	1 1	1 2
2 5	1 3	1 5
3 0	1 6	1 8
3 5	1 9	

B *Relations between the width of the treatment volume and the radioactive material*

1 Separation Width of treatment volume/separation of sources = 1 75 at RI 85 % and 1 90 at RI 70 %

2 Active length The width of the treatment volume remains almost independent of the active length for the same separation of the sources

C *Relations between thickness of treatment volume and radioactive material*

1 Separation Thickness of treatment volume/separation of sources = 0 5 at RI 85 % and 0 85 at RI 70 %

2 Active length The thickness of the treatment volume increases slightly as the active length of the sources increases from 1 to 10 centimetres from 0 46 to 0 59 at the 85 % isodose and from 0 77 to 0 92 at the 70 % isodose)

Inter relations between the dimensions of the treatment volume

1 Width and thickness

From relations B-1 and C-1 above it is evident that width and thickness are linked within the limits studied thus width/thickness at RI 85 % = 3 5 and at RI 70 % = 2 3

There is some variation in these values as the active lengths vary from 1 to 10 centimetres from 3 9 to 3 0 at the 85 % isodose and from 2 5 to 2 1 at the 70 % isodose

2 Length and width

There is a useful relation between the length and the width of the treatment volume If the width of the treatment volume is small the isodoses are such that the width is numerically greater than the length implying that the sources may be more effectively placed perpendicular to the long axis of the treatment

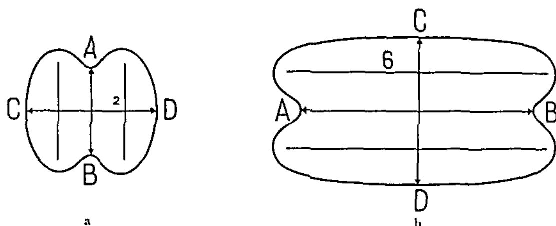


Fig. 4. Relation between length and width of a treatment volume enclosed by the 70 % reference isodose. a) With 2 cm long sources separated by 1.46 cm. The treatment volume is only 1.8 cm long (AB) and 2.7 cm wide (CD). b) With 6 cm long sources separated by 1.68 cm. This situation is reversed: length of treatment volume 7.3 cm (AB) and width 3.2 cm (CD).

volume. After a certain critical combination of the length of the treatment volume and the separation of the sources this situation is reversed. In practice, this concept is of value only for sources up to 4 cm long; with greater active lengths, the separation which would be necessary to make the width of the treatment volume *its largest dimension would be unacceptably great (Table 1).*

Fig. 4 shows the situation as it applies to 2 cm and 6 cm long sources. Table 1 provides more specific data in the clinically important region. The separation values set out in the table are those which correspond to treatment volumes whose length and width are equal at the values shown. Thus if the desired actual separation is less than the value shown, the sources should be placed as in Fig. 4b but if it exceeds this value as in Fig. 4a. Treatment volumes less than 2 cm long are always treated with transverse sources (Fig. 4a) and those more than 3.5 cm long always with longitudinal sources.

3. *Thickness of treatment volume and diameter of the high dose zone*

If one takes the smallest treatment volume (active length of sources 1 cm, separation 0.8 cm, reference isodose 85 %) and the largest volume (active length 10 cm, separation 2.1, reference isodose 70 %), then for the same linear activity (but a different basal dose) the respective diameters of the high dose zones are as follows:

	Thickness	*Diameter of high dose zone*
Smallest volume	0.36 cm	0.35 cm
Largest volume	1.80 cm	0.97 cm

Table 2

Active length of sources (cm)	Separation of sources (cm)			
1	0 8	0 9	1 0	1 1
2	1 1	1 2	1 3	1 3
3	1 2	1 3	1 4	1 6
4	1 2	1 3	1 5	1 7
5	1 3	1 4	1 6	1 8
6	1 3	1 4	1 6	1 9
7	1 3	1 5	1 7	1 9
8	1 3	1 5	1 7	2 0
9	1 3	1 5	1 7	2 0
10	1 3	1 5	1 8	2 1
B sal dose (rad/h) for a l ear activity of 1 0 mC /cm using irid um 192	40	35	30	25

Discussion

We have taken the active lengths of the sources to vary from 1 to 10 centimetres because these are the usual lengths required in practice It might well be necessary to increase the length beyond 10 cm for special reasons if so the separation of two sources should still not exceed 2 1 cm

The upper and lower limits which we have chosen for the separation of sources are justified as follows The upper limit 2 1 cm corresponds to a high dose zone almost 1 cm in diameter with 10 cm long sources and using the 70 % isodose In the present state of our experience we do not like to exceed this diameter and we have the impression that tissue repair becomes much more difficult (with excessive risk of necrosis) when a cylinder of tissues receiving more than 15 000 rad does exceed it The lower limit of separation is justified by the fact that very narrow thin lesions are best treated by a single line source

The separations between the sources which we have selected for study have been greater as the active lengths have increased for these three reasons

Physical fact the diameter of an isodose round a radioactive line source increases more rapidly with increase in active length the further the isodose considered is situated from the source (PIERQUIN & DUTREIX 1967)

Technical reason it is difficult to ensure that long wire sources are parallel and there is a greater risk of the hot and cold areas of the separations becoming too small

Clinical practice the thickness of the treatment volume tends to increase with its length, and this implies a greater separation

The separation has been further limited in order to ensure that the dose rate falls within reasonable limits for the linear activity of source commonly used In practice, we try to limit the separation to the values shown for each active length in Table 2 The resulting basal dose rates for iridium 192 wire of linear activity 1 0 mCi/cm are shown at the top of each column It is emphasized that these limits, with the exception of the minimum (0 8 cm) and the maximum (2 1 cm) values justified above are, at present, purely empirical

The dimensions which we have chosen to define the treatment volume are useful in practice, though it must be remembered that in reality this volume has a complex outline somewhat resembling an ellipsoid The three dimensions chosen have this in common they all pass through the centre of the treatment volume where the basal dose is calculated (Fig 3) The radiotherapist must however remember that the given dimensions do not describe a cuboid form, and must plan his treatment volume to the existing target volume accordingly

From our data, the smallest volume suitable for treatment by two straight parallel sources measures 0 4 cm × 0 7 cm × 1 4 cm and the largest volume 1 8 cm × 4 1 cm × 9 0 cm Because of the limits, which are imposed for the reasons mentioned above, on the separation of sources, however, not all volumes lying between these outside values may be so treated Whether or not any given volume is acceptable can be determined from the relationships set out above and in Table 2 If the width limit is exceeded additional lines are required in the same plane, and if the thickness limit is exceeded more planes are required

Although it would be possible to propose rules for the optimum distribution of two straight parallel sources in treatment volumes suitable for treatment by them, this is better left until a study of the more complex arrangements which are useful in practice has been completed

Conclusions

The systematic study now reported upon, concerned with the dosimetry around two straight, parallel radioactive sources of equal length, formed the first stage in a theoretical analysis of the methods used in our system of curietherapy The aim of the analysis has been to provide information necessary for the formulation of rules for a preliminary distribution plan which will enable the techniques used to be applied to the best physical advantage Extensive calculations have been made by the aid of a computer Simple relationships between the dimensions of the treatment volume and the disposition of the radioactive material were revealed These relationships will form a fundamental starting point for the study of more complex arrangements

SUMMARY

A systematic study of the dosimetry around two straight parallel radioactive sources of equal length has been made by the aid of a computer with the aim to provide basic information for setting up preliminary distribution plans enabling the techniques used in curietherapy to be applied to the best advantage Simple relationships between the three dimensions of the treatment volume and the disposition of the radioactive material could be established and these will form the fundamental starting point for a study of more complex arrangements

ZUSAMMENFASSUNG

Eine systematische Studie der Dosimetrie um zwei gerade und parallele radioaktive Quellen von gleicher Länge wurde mit Hilfe von Rechenautomatik durchgeführt Die Untersuchung hatte zum Zweck fundamentale Auskunft zu ermitteln die zur vorläufigen Dosisplanierung geeignet ist um die Technik der Curietherapie am besten auszunutzen Es wurden einfache Beziehungen zwischen den drei Dimensionen des Behandlungsvolumen und der Applikation des radioaktiven Materials erreicht die als fundamentaler Operationsbasis beim Studium von komplizierteren Anordnungen verwendet werden sollen

RÉSUMÉ

Une étude systématique de la dosimétrie autour de deux sources radioactives droites et parallèles de même longueur a été effectuée et constitue le premier chapitre des applications pratiques d un niveau système de curiethérapie Des relations simples ont été mises en évidence entre les trois dimensions du volume traité et le matériel radioactif Ces relations constituent une base de départ fondamentale pour les études dosimétriques de dispositifs radifères plus complexes

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FROM DEUTSCHES KREBSFORSCHUNGSZENTRUM, INSTITUT FUR NUKLEARMEDIZIN, HEIDELBERG, WEST GERMANY

UPTAKE OF COLLOIDAL CHROMIC PHOSPHATE IN THE MEDIASTINAL LYMPH NODES

Therapeutic possibilities

by

L. J. ANGHILERI

Reports on the uptake of radioisotopes in the lymph nodes, and in the mediastinal lymph nodes in particular, are scarce, as compared to the extensive literature in the whole field of nuclear medicine. WALKER (1950) demonstrated that the phagocytes of the lymph nodes are very efficient in removing large particle colloids injected into the afferent lymphatic vessels. A few years later, HAHN et coll. (1953) described the therapeutic use of intrabronchially instilled silver coated radiogold, but the extremely variable distribution of radioactive material in tissues, and the widely differing activities exhibited by the different lymph nodes, would seem to leave the efficacy of this technique in doubt. HO CHOI et coll. (1965) tested intrapleural injection of radiogold as a scanning technique for use in the study of the mediastinal lymphatics in animals. Their results indicated that sufficient time must be allowed for the radiocolloid to enter the lymphatics, the activity did not exceed 5 per cent of the dose injected. MULLER (1956), after intraperitoneal injection in a patient, reported that a considerable amount of radiogold was detected in the mediastinal lymph nodes.

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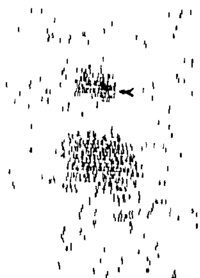
Table 1

Radioactivity distribution of ^{51}Cr labelled chromic phosphates in per cent of the injected dose (particulate chromic phosphate particle size 0 6 to 2 μ colloidal chromic phosphate particle size 0 1 to 0 2 μ)

	At 1 day after injection				At 7 days after injection			
	Particulate chromic phosphate		Colloidal chromic phosphate		Particulate chromic phosphate		Colloidal chromic phosphate	
	Intravenous	Intraperitoneal	Intravenous	Intraperitoneal	Intravenous	Intraperitoneal	Intravenous	Intraperitoneal
Liver	46 6	6 6	85 9	50 5	47 2	4 6	86 8	64 4
Spleen	4 5	1 7	2 6	1 3	5 4	1 1	2 4	1 4
Lung	8 0	0 1	0 2	0 1	1 9	0 8	0 1	0 1
Skeleton	4 0	0 4	2 9	0 3	7 8	0 3	0 9	1 9

no quantitative estimate of the distribution in other regions of the body was published

A new radiocolloid for intracavitary radiotherapy has previously been described (ANGHILERI et coll 1967) This compound of gelatin chromic phoshate has all the characteristics of a true colloidal solution (particle size 0 1 to 0 2 μ)



Scintigram showing the radioactive distribution at 24 hours after intraperitoneal injection of 50 μCi of Cr 1 belled colloidal chromic phosphate Two regions of uptake may be noted I er-spleen pancreas area and the thymus med ast nal s lymph nodes

FROM DEUTSCHES KREBSFORSCHUNGSZENTRUM, INSTITUT FUR NUKLEARMEDIZIN,
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Table 2 *(cont.)*

	After 7 days	
Papain and colloidal chromic phosphate injection after 10 minutes	Colloidal chromic phosphate	Colloidal chromic phosphate and papain injection after 20 20 minutes
1 96	0 81	1 47
22 88	27 87	14 43
3 36	0 98	2 47
2 59	1 08	1 34
19 79	6 97	5 08

proposed as a therapeutic agent (MESNARD & MADELON 1960, EMELE et coll 1966) On this basis an attempt has been made to test the possibility of increasing the particle size in situ in order to obtain a higher uptake in the lymph nodes With this purpose in mind other groups of animals were injected with 2 5 mg of papain in 2 5 ml av saline before or after the radiocolloid injection and radioactivity counting was performed in the same fashion

The typical distribution of both types of chromic radiophosphate after intravenous and intraperitoneal injections are recorded in Table 1 the radioactivity distribution 24 hours after injection of the radiocolloid is demonstrated by the scintigram p 203 It may be noted that there are two regions of radioactivity uptake the liver spleen pancreas area and the area of the thymus-mediastinalis lymph nodes (indicated by the arrow) After dissection the separated counting in the mediastinal lymph nodes and the thymus showed a ratio of approximately 70 1 which is an indication that most of the radioactivity is taken up by the lymph nodes The radioactivity values in different organs and tissues at respectively 1 day and 7 days after intraperitoneal injection of colloidal chromic phosphate are given in Table 2 the effects of pre and post colloidal injections of papain are also recorded in this table

The radioactivity uptake of the mediastinal lymph nodes (Table 2) is 4 times higher after colloidal chromic phosphate injection than after the particulate type of administration It should be remembered that the particulate chromic phosphate has a wide range of particle size 0 6 to 2 μ with a predominating size of over 1 μ (ANGHILERI 1965) Some of these particles succeed in reaching the thoracic

Table 2

Radioactivity distribution (in per cent) after injection of ^{51}Cr labelled chromic phosphates and the effects of intraperitoneal injection of papain (all percentages are means of values from three animals)

	After 24 hours		
	Particulate chromic phosphate	Colloidal chromic phosphate	Colloidal chromic phosphate and papain injection after 20 minutes
Spleen	4 13	2 83	2 12
Liver	6 83	44 73	29 74
Intestine	0 24	1 68	4 14
Mesentery	0 32	1 43	2 24
Mediastinal lymp nodes	2 30	9 32	6 80

The uptake of radiocolloids is also largely affected by the route of administration Colloids of relatively great particle size are mainly deposited in the liver and spleen after intravenous injection, while colloids of smaller particle size are deposited *primarily in the bone marrow and spleen and secondarily in the liver* (SCHUBERT 1951) When administered intraperitoneally the particulate form of chromic phosphate is pocketed in various areas of the peritoneum, or filtered out by the first lymph nodes encountered because of the too large particle size, whereas the colloidal form is carried over to the lymphatic system The larger particles originally present in its size spectrum or formed in vivo by aggregation of smaller particles are trapped by the first line of lymph nodes, and the *remainder go into the thoracic duct, with posterior incorporation into the* blood circulation and final removal by the reticulo endothelial system liver, spleen and bone marrow

This paper is a report on experimental work carried out for investigating the fate of ^{51}Cr labelled colloidal chromic phosphate after intraperitoneal injection in rats Adult albino rats weighing 250 grams were injected with 50 μCi of the agent and sacrificed after 1 day and 7 day intervals The radioactivity was counted with a well type scintillation counter (Gamma Guard Tracerlab) in various organs and tissues

In the preliminary experiments in vitro tests had shown the colloidal chromic phosphate to precipitate rapidly and completely through the hydrolytic action of papain The physiologic effects of this enzyme have been intensively studied (HAKIN & PETERS 1962, MORARD et coll 1963, SPICER & BRYAN 1958) and

SUMMARY

The uptake of radioactive colloidal chromic phosphate in the mediastinal lymph nodes was studied after intraperitoneal injection in rats A significant uptake approx 9 % was noted and this can be increased to approx 19 % by pre injection of papain The wider range of action of the new compound of this colloid offers advantages over the particulate form of chromic phosphate for the prophylactic and therapeutic irradiation of tumor cells

ZUSAMMENFASSUNG

Die Aufnahme von radioaktivem kolloidalem Chrom Phosphat in den mediastinalen Lymphknoten nach intraperitonealer Injektion in Ratten wurde studiert Signifikant war die beobachtete Aufnahme von 9 und dieser Wert konnte mittels Pre Injektion von Papain bis auf 19 % erhoht werden Der grossere Wirkungsbereich dieser neuen Kolloidenverbindung erbietet Vorteile gegenuber der partikularen Form des Chrom Phosphats besonders bei der prophylaktischen und therapeutischen Bestrahlung von Tumorzellen

RÉSUMÉ

L auteur a etudie la fixation du phosphate de chrome colloidal radioactif dans les ganglions lymphatiques mediastinaux apres injection intrapéritonéale sur des rats Il a constaté une fixation importante d environ 9 % qui peut augmenter jusqu a 19 % environ par injection prealable de papaine Le plus large domaine d action de cette nouvelle preparation colloidale presente des avantages sur la forme en particules du phosphate de chrome pour l irradiation prophylactique et therapeutique des cellules tumorales

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duct and are later phagocytized by the mediastinal lymph nodes In the case of the colloidal type, the range of particle size is much lower (0 1 to 0 2 μ), permitting a larger amount to enter the thoracic duct and later the blood circulation The radioactivity uptake in the liver corroborated this assumption The high increase of radioactivity in the mediastinal lymph nodes when papain was injected prior to the colloid (from 9 3 % to 19 3 %) may be explained by an increase in particle size due to enzymatic action It converts the too small particles of the radiocolloid into particles more easily trapped and phagocytized by the lymph nodes As may be seen form Table 2, this morphologic change provokes an increase in the lymph node uptake, with a corresponding decrease in the liver A smaller effect was noted when papain was injected after the administration of the colloid Presumably, the time elapsed between colloid injection and papain administration was long enough to cause migration of the small particle sized colloid without being affected by the enzyme

Despite the large amount of radioactivity deposited in the liver, the dose of radiation is considerably less than for the lymph node We use the formula

$$D = 73\ 8\ C \times \bar{E} \times T$$

in which C=concentration (μCi/gram), $\bar{E}$=0 70 MeV (for ^{32}P), and T=10 days (effective half life), and consider the radioactivity distribution in the fourth column of Table 2 to be the same as for ^{32}P labelled colloidal chromic phosphate The dose delivered to the liver and the mediastinal lymph nodes after intraperitoneal injection of 100 μCi will then be

$$d_{\text{lymph node}} = 199\,408 \text{ rad}$$
$$d_{\text{liver}} = 929 \text{ rad}$$

This calculation provides an estimate of the high dose of strong beta radiation delivered to the lymph node

ZIEDMAN (1955), after injection of tumor cells in the mediastinal lymph glands, demonstrated a pathway for mediastinal node involvement The similarity between the radiocolloid transport by the lymph stream and the lymphatic spread of tumor cells, emphasizes the possibilities of this radiocompound for prophylactic irradiation

After intralymphatic injections of particulate chromic phosphate (particle size 0 5 to 1 5 μ) BURGER (1964) found that most of the radioactivity was deposited in the lymph node closest to the site of injection Contrary to this limited range of action, the colloidal chromic phosphate after intracavitary injection permits prophylactic or therapeutic irradiation (when labelled with ^{32}P) in a wider area of the lymphatic system

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COMBINED EFFECT IN THE RADIOLOGIC AND IMMUNOLOGIC TREATMENT OF A MALIGNANT HOMOGRAFT

by

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Many investigations on the radiation dose response relationships in various lines of mammalian cells both benign and malignant have been reported Since PUCK & MARCUS (1956) reported on the effect of roentgen irradiation of single mammalian cells tested by a colony formation technique in vitro, in vitro studies have been carried out in order to elucidate mainly the cell intrinsic character of the radiosensitivity The influence of peripheral factors on cell radiosensitivity have been analysed mainly by in vivo studies since HEWITT & WILSON (1959) published their in vivo culture method WHITMORE & TILL (1964) stated that normal and malignant mammalian cells derived from different sources provoked about the same response to ionizing radiation WILLIAMS & TILL (1966) reported that newly transformed cells derived from polyoma infected cultures of rat embryo cells in vitro and the transformed cell lines were characterized by D_0 values that did not differ significantly from those obtained for the original cells although the radiosensitivities of some of these cell lines after more than 35 weeks of culture in vitro yielded signifi

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MORARD J C, HALPERN B N and ROBERT L Pathological and biochemical changes and immunological modifications determined in the rabbit by repeated injection of papain C R Acad Sci (Paris) 256 (1963) 1169

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SCHUBERT J Estimating radioelements in exposed individuals Part I Radioelement metabolism Nucleonics 8 (1951), 13

SPICER S S and BRYANT J H Effect of intravenous injection of papain Amer J Path 34 (1958) 61

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investigation was 2×10^4 per ml The prepared cell suspension was divided into 1 5 ml portions for each culture test tube and kept unmoved at 37 C for seven days (monolayer stationary culture)

In vivo culture method and host animals Our diffusion chamber technique has been described in detail elsewhere (KANO 1965) and summarized diagrammatically (KANO 1967) The porosity selected for the millipore filters was 0 22 μ these were sealed to the upper and lower surfaces of each acrylite plastic diffusion chamber with 1 plastic acetone glue The initial cell concentration of the suspension prepared for the in vivo dose response investigation was 25 × 10^4 per ml of which 0 2 ml were injected into eac i autocla ed diffusion chamber through the small hole radially oriented through th chamber wall and then closed with paraffin The hosts were male mice of the dd/YF strain 80 to 120 days old in each of which a diffusion chamber was surgically implanted intraperitoneally for 9 days the dd/YF mice from the Funabashi farms were hou ed individually Conventional pellets of mouse feed and water were supplied ad libitum

Immunization procedure Some of the dd/YF mice were immunized with 3×10^6 Ehrlich cells and others with dd/YF mouse liver tissue 0 4 g by wet weight per mouse

Male white rabbits were also immunized with either 10^7 Ehrlich cells or dd/YF mouse liver tissue 1 7 g by wet weight per rabbit once a week for five consecutive weeks The Ehrlich cells used as ant gen were homogenized or irradiated with 3 000 R (see under heading irradiation procedure) and the dd/YF mouse liver tissue employed as the other n en s s homogenized One millilitre of Freund s complete adjuvant for each mouse and 2 ml for each rabbit were added to the antigens before subcutaneous injection Some of the immunized mice were used as hosts for the diffusion chamber implantation and others were cardiopunctured for antisera collection 10 days after immunization The immunized rabbits were also cardiopunctured for antisera collect on a week after the last immunization

Cytolysis procedures Two procedures were undertaken as follows

1 The Ehrlich cells 10^5 in number were suspended in 1 ml of the culture medium added to 0 1 ml of complement (guinea pig serum) which was obtained in lyophilized form for each culture test tube The inacti ated (56 C 30 min) antiserum of either the mice or the rabbits was added to each test tube in 10 1 0 1 and 0 01 volume per cent of the cell suspension The test tubes re incubated for one day at 37 C whereafter the number of intact cell nuclei were counted The control experiments were undertaken in the same manner with fresh antiserum without the complement or with inactivated antiserum with fresh serum of non immunized dd/YF mice

2 The Ehrlich cells were cultured in sterilized small square bottles 15 mm × 15 mm × 3 mm one of the inside walls of which was partly covered with a small piece of coverslip glass 8 mm 20 mm in s ze Microscopic observation of the cytolysis of the Ehrlich cells was scheduled as follows The bo tles were placed on their sides and the coverslip glasses closely fitted to the lower interior surfaces The initial concentration of the Ehrlich cell suspension prepared for th experim nt was 10 per millilitre This cell suspension was divided into 1 ml for each bottle After being cultured stationary for 1 day at 37 C a monolayer of the cultured Ehrlich cells developed Some of the bottles were exposed to 200 R and 3 hours later 0 1 ml of the complement solution and 0 1 ml of the anti Ehrl ch cell serum of the dd/YF mice or of the rabbits respectively were added to some of these exposed and unexposed bottles The small p eces of coverslip glass with the mounted monolayered Ehrlich cells were taken out 15 30 45 60 min 2 3 4 5 hrs and 1 2 and 4 days respectively after being incubated with

cantly lower D_0 values than those for the original cells Comparison between the radiosensitivities of normal and malignant cells yielded relatively small differences

In order to make malignant cells more radiosensitive than benign cells, sensitization of the former *to irradiation by oxygenation* (GRAY *et coll* 1953) and chemical sensitizers (DJORDJEVIC & SZYBALSKI 1960, ERIKSON & SZYBALSKI 1961 and BERRY & ANDREWS 1962) has been undertaken

Several investigations have demonstrated, however, that some inbred lines of animals may react immunologically against the syngenic tumors, since FOLEY (1953) reported on the antigenisity of methylcholanthrene induced sarcomas Tumor specific immunization seems to be another method of modifying the apparent radiosensitivity of neoplasms (SCOTT 1961 and HADDOW 1964)

In the present experiments, the diffusion chamber technique was used, a sort of in vivo culture method, originating from PREHN et coll (1954) and reviewed by AMOS (1961) By this method the inoculated cells within the diffusion chamber are isolated from the host cells The humoral factors may be transfused both ways, from outside to inside the diffusion chamber, and vice versa, and the number of cells can be counted after the scheduled culture in vivo, precisely as cells cultured in vitro Also, a technique of immunologic cytolysis in vitro has been developed in order to investigate the interaction between radiologic and immunologic treatments as revealed in dose response curves for the Ehrlich cells on a cellular level, as well as to analyse the immunologic factor participating in suppressing the apparent Ehrlich cell growth

Materials and Methods

Ehrlich murine ascites tumor cells The cells (obtained from Prof J Sato of the Cancer Institute Okayama University Medical School) were maintained in vitro they were registered with the Japan Tissue Culture Association as *the JIC 11 line*

In vitro culture method The medium for the Ehrlich cell culture was prepared from a modified Hanks solution containing 64 g NaCl 3 2 g KCl 1 6 g $MgSO_4$ $7H_2O$ 1 6 g CaCl 0 18 g KH_2PO_4 0 48 g Na_2HPO_4 $12H_2O$ 8 0 g glucose 0 1 g phenol red and 1 000 ml H_2O and from an A solution containing 800 mg streptomycin sulfate 504 mg penicillin G crystal and 1 000 ml H_2O

These two solutions were prepared beforehand and stored in refrigerator (4 C) for the final mixing The YLH solution (final mixture) contained 0 2 g yeast extract (Difco) 1 0 g lactalbumin hydrolyzate 25 ml modified Hanks solution 0 9 g glucose 0 125 g $NaHCO_3$ 25 ml A solution 150 ml H_2O The YLH solution was filtered with Seitz s filtration apparatus Inactivated calf serum 20 volume per cent was added immediately before the final solution was utilized as in vitro culture medium

The initial cell concentration of the suspension prepared for the in vitro dose response

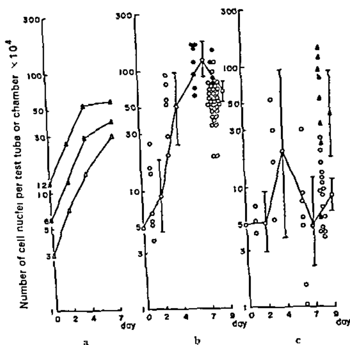


Fig 2 Cont ol growth experiments a) In v tro Three different in tial numbers of c lls we e adopted Each triangle whethe closed or open rep esents aver ge data f om 5 to 10 culture test tubes In tial number 3 × 10 /1 5 ml/tube was selected to be used for n vit o dose response exper ments and is nd cated by open triangles b) In vivo Diffus on chambers and con entional dd/YF m le mice were used adopting the init al numbe 5 × 10 /0 2 ml/chamber Each c cle whether open o closed rep ese ts data obta ned f om one host mouse (these data we e obtained f om seve al series us ng th same e perimental p oce dures) clos d ci cles and cate those obta ned from a single one of these ser es c) In vi o D ffu ion chambers in dd/YF male mice immun zed with e ther the Eh l ch cells or dd/YF mouse l er t ssue and the same in tial number as for (b) Each open ci cle rep esents the data obtained from one host mouse immun zed with the non prolif er t v Eh l ch cells 3 × 10⁴ in number and each closed t iangle d cat s immuni at on with l ver tissue of 0 4 g wet weight
Log mean values w th 95 confidence intervals a e giv n in (b) and (c)

After staining and microscopy no Ehrlich cells could be observed on these coverslip glasses The Ehrlich cells are distinguishable by being remarkably larger than host mouse cells The cell count in the interior of the diffusion chambers revealed that no cells had penetrated the millipore filters in the chambers initially containing only culture medium and in the Ehrlich cell chambers only Ehrlich cells were found The chosen porosity 0 22 μ of the

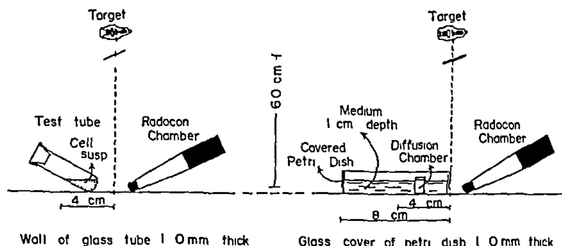


Fig 1 Schematic drawing showing the arrangements for the irradiation procedure

the antiserum complement system These coverslip glasses were then rinsed with physiologic salt solution warmed to 37 C fixed with methanol and stained with Giemsa 1 day after the fixation and observed microscopically

Irradiation procedure The Ehrlich cell suspension was exposed to single doses of roentgen rays for the in vitro experiment in test tubes and for the in vivo experiment within the diffusion chambers immersed in YLH solution in covered Petri dishes (Fig 1)

The physical factors of irradiation were 190 kV 24 mA 1 0 mm Cu and 0 5 mm Al filtration 60 cm target object distance 37 R/min in air and room temperature The roentgen rays were generated by Toshiba s X ray apparatus KXC 18 2A The doses were measured with Victoreen s Radocon Model 575 and Chamber Model 601

Cell counting method In all instances except for the cytolysis experiment the Ehrlich cells after the scheduled incubations were stained by crystal violet in citric acid solution and the number of nuclei counted using the Buerker Tuerk type of haemocytometer The diffusion chamber containing the cultured cells was immersed in the staining solution the millipore filters attached to both surfaces were broken with the tip of a pipette the staining solution was pipetted and then the nuclei in the suspension were counted

Statistical analysis The data obtained in the dose response experiments in vivo were analysed by logarithmic F distribution and the 95 % confidence intervals were estimated

Results

Migration of cultured and host cells through the millipore filters After the implantation of the diffusion chamber for 9 days the host mice were sacrificed, the abdominal wall was opened and the chambers removed Coverslip glasses were mounted by pressing them against the peritoneal membranes of some of the host mice, in which chambers containing the Ehrlich cells had been implanted

Table 3

Number of residual intact Ehrlich cell nuclei after immunologic cytolysis

Relat ve volume of antisera	Intact cell nucle * (× 10)							
	Ant Ehrl ch cell mouse serum				Anti Ehrlich cell rabbit serum			
	Ca es			Mean	Cases			Mean
10	5 5	5 9		5 7	1 3	1 6	1 8	1 6
1	6 ?	6 7	8 6	7 2	3 6	4 2	4 6	4 1
0 1	5 8	13 4	14 1	11 1	4 7	7 1	7 7	6 5
0 01	9 4	9 5	10 3	9 7	9 8	11 6	13 0	11 5

Initial numb f Ehrlich cell nucle 10 × 10

Thus in the conventional hosts the control growth curves both in vitro and in vivo seemed to maintain approximately an exponential growth during the experimental period while the number of surviving cell nuclei of the 9 day culture varied according to the logarithmic normal distribution

Dose responses The dose response curves are presented in Figs 3 and 4 The most remarkable characteristic in these curves is that the dose response curve in the hosts immunized against the Ehrlich cells is displaced downward to run approximately parallel to the curve in the conventional hosts The experimental conditions extrapolation numbers and 37 % survival doses in the straight portions of the dose response curves as slopes (D_0) are given in Table 1 the upper two extrapolation numbers appear to be similar and the third one to be larger than the upper two while the differences in the 37 % doses are probably insignificant

Relationship of initial cell number and suppression rate by immunization Three different initial cell numbers 2 5 5 and 7 5, × 10' (0 2 ml) chamber were adopted for the *in vivo* culture within diffusion chambers for nine days in both the immunized and the control hosts The non irradiated Ehrlich cells were contained in the diffusion chambers Similar suppression rates by the immunization were obtained in the experimental series with each initial cell number by comparing the final cell numbers in the immunized with those in the control hosts (see Table 2)

Cytolysis experiments The Ehrlich cell nuclei in the control yielded a 2 fold increase of the initial cell number after the Ehrlich cell suspension had been incubated for 1 day without complement or antiserum As shown in Table 3

Table 1

Extrapolation numbers and 37 % survival doses in three series of experiments

Conditions		Extrapolation number	37 % dose (slope)
Irradiation	Culture		
In vitro	In vitro	1.3	310 R
In vitro	In vivo in conventional hosts	1.4	275 R
In vitro	In vivo in immunized hosts	2.2	270 R

Table 2

Relationship of initial cell number and suppression rate by immunization

Initial cell number ($\times 10^4$)	Log suppression rate* with 95 % confidence interval
2.5	0.54 ± 0.30
5	0.44 ± 0.07
7.5	0.44 ± 0.07

$$\text{* Suppression rate} = \frac{\text{Relative log survival in the immunized hosts}}{\text{Relative log survival in the control hosts}}$$

millipore filter prevented cell migration, the critical porosity of 0.45 μ may sometimes permit migration of small cells through the filter.

Control growth. All data for the control growth are given in Fig. 2. The number of cell nuclei in the control after 9 days produced a 13 fold increase in the initial cell number in the conventional hosts, an 8 fold increase in the hosts immunized against the isologous liver (closed triangles), but in the hosts immunized against the Ehrlich cells only a 1.7 fold increase (open circles).

In the control growth in vivo, in the hosts immunized against the Ehrlich cells, the number of cell nuclei in the 2, 4, 7 and 9 day cultures were not significantly different from the number of nuclei at the beginning of the culture (Fig. 2c). In the conventional hosts, the Ehrlich cells after 7 day culture showed a higher cell number than those after 9 days. The 9 day growth data, obtained from the same experimental series as for the control growth after 7 days, are shown with closed circles among all the 9 day controls. The growth rate in the control for 7 days *in vitro (open triangles)* gave a similar value to that in vivo for 9 days in the conventional hosts.

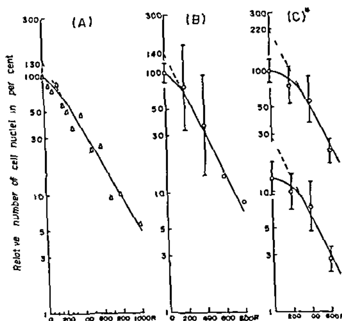


Fig 4 Do e respon e curves a) In vitro The values indicated by open triangles in fig 3a were shifted to values relative to the final number of non irrad ated control g owths for 7 days b) Relative log mean values with 95 confidence intervals were estimated from data given n fig 3b c) The uppe curve represents the estimated log mean values w th 95 confidenc ntervals relative to the final number of the non irradi ted Ehrl h cell growths in the hosts immunized with Ehrlich c lls The lower curve s the s me as the upper curve except that it represents the est mated values relat ve to tho e n the conventional hosts

different periods with the inactivated anti Ehrlich cell rabbit or mouse serum and the complement solution The first damage was observed 15 min after incubation with the rabbit antiserum Longer incubation resulted in more distinct damage to the cytoplasmic portion of the cells

Microscopic observations at 15 min 2 and 4 hrs and at 4 days after incubation with the rabbit antiserum and complement are illustrated in Fig 5 Incubation with the complement solution and without the antiserum resulted in little cytoplasmic damage to the Ehrlich cells as shown in Fig 6 Fig 7 shows the observations 2 and 5 hrs after incubation with the mouse antiserum and complement The incubation of the previously irradiated Ehrlich cells with 200 R three hours before *adding* the mouse antiserum and complement did not result in any cytoplasmic damage greater than that in the non irradiated cells at 5 hrs after the antiserum and complement had been added

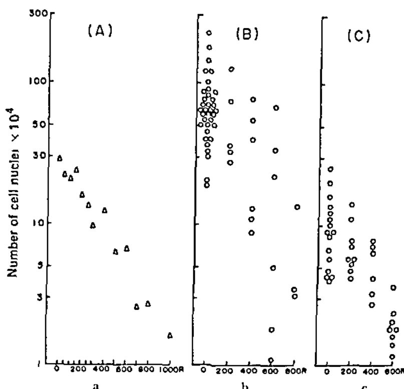
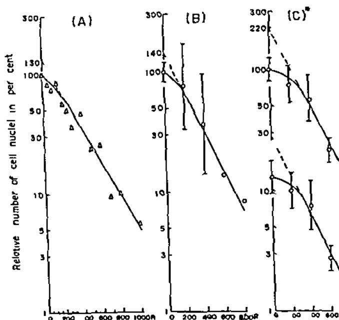


Fig 3 Dose response curves a) *In vitro* Open triangles indicate average final number of Ehrlich cell nuclei after 7 day culture Initial number was 3 × 10 /tubes At beginning of culture the tubes containing the Ehrlich cell suspension were treated with several doses of roentgen irradiation b) *In vivo* Each open circle indicates data of culture for 9 days in diffusion chamber obtained from each of the conventional dd/YF male hosts The Ehrlich cells [illegible] × 10^4 in initial number just before the implantation were treated in the diffusion chamber with several doses of roentgen irradiation c) Same as for (b) except that hosts immunized with 3 × 10 Ehrlich cells 10 days before the chamber implantation were used

the addition of inactivated anti Ehrlich cell mouse or rabbit sera resulted in cytolysis of the Ehrlich cells when the Ehrlich cell suspension was incubated for 1 day with one of these antisera together with the complement, while without complement the addition of these antisera did not seem to result in cytolysis of the Ehrlich cells, neither did the cell number increase when incubated The number of Ehrlich cells not undergoing cytolysis was apt to increase with the decrease in relative volume of the anti Ehrlich cell sera However, this tendency was much more apparent when the Ehrlich cells were incubated with the rabbit antiserum than with that of mice

On the other hand, the morphologic damage of the Ehrlich cells by the antiserum was observed microscopically after they had been incubated for



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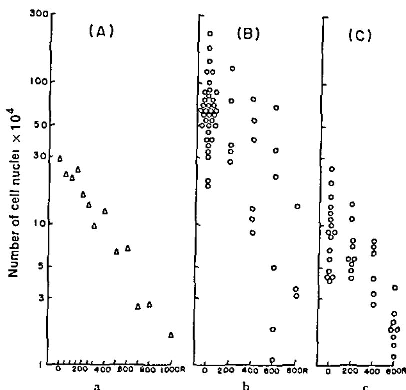


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Fig f Cytolysis of Ehrlich cells Giemsa × f00 Microscopic observations at 2 hours (a) and 3 hours (b) after incubation with complement The cytoplasm is intact

no change in the number of cell nuclei after the 1 day incubation was observed and little cell debris was noted in either of the present experimental systems of cytolysis

Discussion

Character of host resistance factor transfusible into diffusion chamber Despite the cell impermeability of 0 22 μ millipore filter as shown in the results and demonstrated by NETTESHEIM et coll (1966) the apparent Ehrlich cell growth within the diffusion chamber was suppressed when cultured in the host immunized against the Ehrlich cells as shown in Fig 2c It was therefore considered that some humoral factor in the ascites fluid of the immunized host was transfusible into the diffusion chamber After 9 day culture no significant difference was found between the numbers of the cell nuclei in the conventional hosts and in those immunized against the isologous liver (Fig 2b) whereas the difference in the number of cells between hosts immunized against the isologous liver and those immunized against the Ehrlich cells was significant (Fig 2c) Thus in the present in vivo experimental system the humoral factor in the immune ascites fluid seemed to be the immunologic reagent against the Ehrlich cells

The prepared anti Ehrlich cell serum of dd/YF mice is considered to be an isoantiserum while that of rabbits is probably a heteroantiserum When the Ehrlich cells were incubated without the complement neither antisera produced any major cytolysis of the Ehrlich cells The higher the concentration of the antisera incubated with the complement the lower was the number of Ehrlich cells that apparently remained intact Thus in the present in vitro

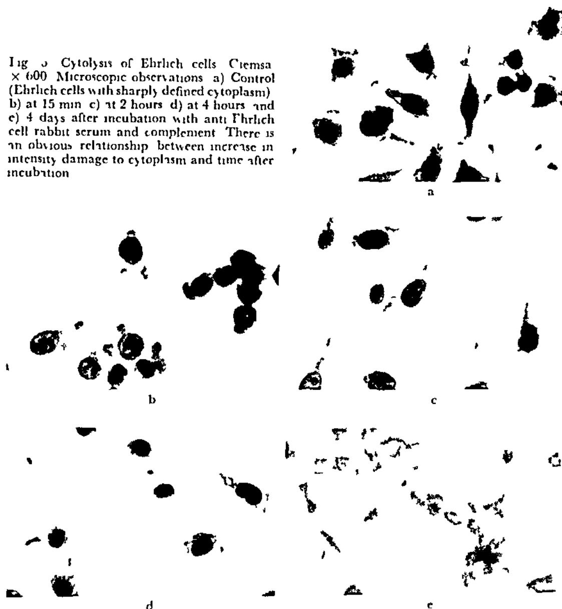


Fig. 5. Cytolysis of Ehrlich cells. Giemsa × 600. Microscopic observations. a) Control (Ehrlich cells with sharply defined cytoplasm), b) at 15 min, c) at 2 hours, d) at 4 hours and e) 4 days after incubation with anti-Ehrlich cell rabbit serum and complement. There is an obvious relationship between increase in intensity damage to cytoplasm and time after incubation.

Cytolysis was distinctly observed within a rather short period of incubation with the heteroantiserum complement system but was not noteworthy with the isoantiserum complement system. The damage to the cytoplasmic portion in these experiments was observed morphologically before the damage to the cytonucleic portion.

The mouse isoantiserum seems to be characteristic in suppressing the apparent Ehrlich cell growth rather than in producing any marked cytolysis, because



Fig 6 Cytolysis of Ehrlich cells Giemsa × 600 Microscopic observations at 2 hours (a) and 3 hours (b) after incubation with complement The cytoplasm is intact

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Fig. 7. Cytolysis of Ehrlich cells. Giemsa. × 600. Microscopic observations at 2 hours (a) and 5 hours (b) after incubation with anti Ehrlich cell dd/YF mouse serum and complement. In (c) and (d) the Ehrlich cells were treated with *200 R* at *3 hours* before the incubation. *There is less* damage of cytoplasm as compared with fig. 5.

experimental system, the complement fixation reaction seemed to be the most probable mode of immunologic cytolysis. However, when the Ehrlich cells were incubated with much diluted anti Ehrlich cell mouse serum, 0.01 volume per cent together with the complement, the apparent number of Ehrlich cells neither increased nor cytolytically decreased, as indicated in Table 3. With this concentration of the antiserum, two possibilities may explain the cell number kinetics: (1) the decrease in the cell number by cytolysis and its increase by proliferation were apparently neutralized by each other or (2) the Ehrlich cell proliferation was suppressed and the cytolysis was slight. The latter possibility is rather probable, because cells, damaged by cytolysis or cell debris were not distinctly observed microsopically after incubation with this concentration of antiserum. AMOS & WAKEFIELD (1958) have described an iso

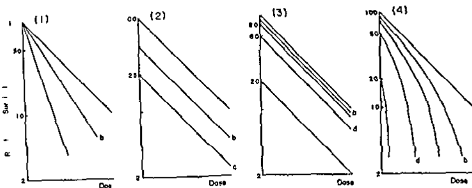


Fig 8 The fou theoret cal formulas and their curves

(1) represents $N = N^{-K A_{imm} D}$ For the respective curves A_{imm} is in (a) = 1 in (b) = 1 5 and in (c) = 3

(?) represents $N = N B_{imm} e^{-K D}$ For the respect ve curves B_{imm} is in (a) = 1 in (b) = 0 5 and in (c) = 0 25

(3) $N = (N - N_{imm}) e^{-K D}$ (a) $N_{imm} = O$ (b) $N_{imm} = 0 1$ N (c) $N_{imm} = 0 2$ N (d) $N_{imm} =$ 0 4 N (e) $N_{imm} = 0 8$ N

(4) $N = N e^{-K D} - N_{imm}$ (a) $N_{imm} = O$ (b) $N_{imm} - 0 1$ N (c) $N_{imm} = 0 2$ N (d) $N_{imm} =$ 0 4 N (e) $N_{imm} = 0 8$ N

immune ascites fluid in which hemagglutinating neutralizing and protective effects were demonstrated Cytotoxic effects of iso immune sera against a lymphoma cell line could be demonstrated with a variety of techniques both in vitro (GORER & O GORMAN 1956) and in vivo (GORER 1942 and GORER & AMOS 1956)

Control growth in vivo in immunized mice The number of cell nuclei in the hosts immunized against the Ehrlich cells did not change significantly during the 9 days of culture (Fig 2c) It was expected that the control growth curve would display a more or less moderate slope the number of cell nuclei in the 4 day culture varied however and included cases that were as well proliferated as those in the conventional hosts The most probable reason for the variation of the cell number in the 4 day culture is that until the transfusion of immune ascites fluid into the chamber has not been adequately established after the operative implantation of the chamber some of the apparent 4 day growths are not quite suppressed by the immunization This explanation would be in accord with the data of the cytolysis experiments in vitro in which the Ehrlich cells were adequately exposed to the antiserum and complement the cytoplasmic portion then being damaged and the apparent growth suppressed within one day

Possible theoretical dose response formulas under the cooperative condition between irradiation and immunization The results obtained seem to indicate that irradiation and immunization suppress the apparent Ehrlich cell growth, simultaneously but probably in different manners Theoretical formulas for this joint action are proposed in the following (Fig 8)

(1) $N = N_o\, e^{-K\, A_{Imm} D}$, (2) $N = N_o\, B_{Imm}\, e^{-K\, D}$, (3) $N = (N_o - N_{Imm})\, e^{-K\, D}$,
(4) $N = N_o\, e^{-K\, D} - N_{Imm}$

where

N surviving cell number
N_o initial cell number
N_{Imm} number of cells destroyed by immunological reaction
K cell intrinsic radiosensitivity coefficient
A_{Imm} and B_{Imm} the coefficients by which immunological reaction modifies these formulas, and
D the irradiation dose

These formulas are applicable unmodified, when cell proliferation kinetics can be excluded experimentally, as with the colony formation method When cell proliferation kinetics are included, as in a cell counting method, N_o should be multiplied by the growth rate, a function of the irradiated dose, if the growth rate is dose dependent However, as observed in the present cytolysis experiments, incubation with the iso antiserum suppressed the cell growth Among the groups of cells, which were irradiated with various doses and cultured either in the immunized or in the conventional hosts, the postulation of a non proliferating cell system or equivalent growth rates may explain these theoretical formulas simply as follows

In *formula (1)*, A_{Imm} modifies the original coefficient K, to the apparent coefficient $K \times A_{Imm}$ When A_{Imm} is larger than 1, cells are sensitized by the immunization, when A_{Imm} is smaller than 1, cells are protected from irradiation by the immunization, and when A_{Imm} is $= 1$, the immunization has no effect on the apparent radiosensitivity When cells are not irradiated, the existence of immunization in this mode has no effect it may be so weak that the apparent cell growth may not be damaged by the immunization alone The ratio inactivation to intensity of immunization is constant within a certain range, regardless of the initial cell number N_o, as seen in Fig 9—(1)

In *formula (2)*, the immunization multiplies the initial cell number by the coefficient B_{Imm} When B_{Imm} is smaller than 1, N_o is reduced In this mode, the ratio inactivation to intensity of immunization is constant within a certain range re ardless of the initial cell number N_o, as shown in Fig 9—(2)

In *f* , o is directly reduced by N_{Imm}, and the intact cells, i e (N_o n damaged by irradiation N_{Imm} in this mode for N_o >

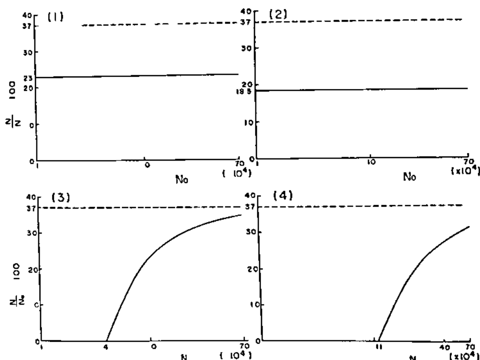


Fig 9 Relat onsh p between N and Λ/Λ in th four theoretical formulas shown in fig 8
(1) When A_{imm} is 1 5 and th cells we e t e t d in vitro w th the or ginal 37 dose D in vi o in c n ent on l hosts N/N 100 is constant rega dles of the variety of the in t al number N accord g to theoret cal formul (1)
(2) When B_{imm} is 0 5 and the cells are treat d with D N/N × 100 is also constant regardless of the ariety of the n t al number N a cording to theoret cal formula (2)
(3) When N_{imm} i 4 × 10 and constant acco ding to the intensity of the immun zation but not relat e to N and the cells are treated with D N/N × 100 is as the curve in fig 9 (3) according to theo et c l formula (3)
(4) When cond t ons are the me a n (3) the urve n fig 9 (4) is accord ng to theo etical formula (4)

N_{imm} is independent of the initial number N_0 within a certain range but dependent on the intensity of the immunization However Λ/Λ_0 varies according to the variation of Λ as shown in Fig 9—(3)

In *formula (4)* N_{imm} is reduced from the survivals after irradiation i e ($N \times e^{-kD}$) N/Λ_0 varies according to the variation of Λ_0 as shown in Fig 9—(4)

Among these four formulas formula (2) and formula (3) generate inactiva tion curves similar to those obtained in the present experiments with the im munized hosts Formula (3) may be neglected because the initial number of Ehrlich cells 2 5 × 10⁴ for one immunized mouse manifested well proliferated

Possible theoretical dose response formulas under the cooperative condition between irradiation and immunization The results obtained seem to indicate that irradiation and immunization suppress the apparent Ehrlich cell growth, simultaneously but probably in different manners Theoretical formulas for this joint action are proposed in the following (Fig 8)

(1) $N = N_0\ e^{-K\ A_{\mathrm{imm}} D}$, (2) $N = N_0\ B_{\mathrm{imm}}\ e^{-K\ D}$, (3) $N = (N_0 - N_{\mathrm{imm}})\ e^{-K\ D}$, (4) $N = N_0\ e^{-K\ D} - N_{\mathrm{imm}}$

where

- N surviving cell number
- N_0 initial cell number
- N_{imm} number of cells destroyed by immunological reaction
- K cell intrinsic radiosensitivity coefficient
- A_{imm} and B_{imm} the coefficients by which immunological reaction modifies these formulas, and
- D the irradiation dose

These formulas are applicable unmodified, when cell proliferation kinetics can be excluded experimentally, as with the colony formation method When cell proliferation kinetics are included, as in a cell counting method, N_0 should be multiplied by the growth rate, a function of the irradiated dose, if the growth rate is dose dependent However, as observed in the present cytolysis experiments, incubation with the iso-antiserum suppressed the cell growth Among the groups of cells, which were irradiated with various doses and cultured either in the immunized or in the conventional hosts, the postulation of a non proliferating cell system or equivalent growth rates may explain these theoretical formulas simply as follows

In *formula (1)*, A_{imm} modifies the original coefficient K to the apparent coefficient $K \times A_{\mathrm{imm}}$ When A_{imm} is larger than 1, cells are sensitized by the immunization, when A_{imm} is smaller than 1, cells are protected from irradiation by the immunization, and when A_{imm} is $= 1$ the immunization has no effect on the apparent radiosensitivity When cells are not irradiated, the existence of immunization in this mode has no effect, it may be so weak that the apparent cell growth may not be damaged by the immunization alone The ratio inactivation to intensity of immunization is constant within a certain range, regardless of the initial cell number N_0 as seen in Fig 9—(1)

In *formula (2)*, the immunization multiplies the initial cell number by the coefficient B_{imm} When B_{imm} is smaller than 1, N_0 is reduced In this mode, the ratio inactivation to intensity of immunization is constant within a certain range regardless of the initial cell number N_0, as shown in Fig 9—(2)

In *formula (3)*, N_0 is directly reduced by N_{imm} and the intact cells, i e $(N_0 - N_{\mathrm{imm}})$, are then damaged by irradiation N_{imm} in this mode, for $N_0 >$

modified by adding a factor P which is a function of the suppression coefficient for growth rate by the immunization as follows

$$2^{P_{imm}}/2^{P_o} = 2^P = e^{-Q}$$

where P_o and P_{imm} = the number of cell divisions estimated in the apparent Ehrlich cell number in the conventional and immunized hosts respectively, in which it is assumed that the cells proliferated homogeneously

$$\lambda = \lambda_0 e^{k A_{imm} D} e^{-Q} \tag{1}$$
$$= \lambda_0 e^{-k A_{imm}(D + Q/k A_{imm})} = \lambda_0 e^{-k A_{imm} D}$$

where $D = D + Q/k A_{imm}$

$$\lambda = \lambda_0 B_{imm} e^{-k(D+Q/k)} = \lambda_0 B_{imm} e^{-k D} \tag{2}$$

where $D = D + Q/k$

$$\lambda = (\lambda_0 - \lambda_{imm}) e^{-k D} \tag{3}$$

$$\lambda = \lambda_0 e^{-k D} - \lambda_{imm} \tag{4}$$

Thus these four further modified formulas give curves which were shifted parallel from right to left on the semilog diagrams shown in Fig 10 representing c to c (1) b to b (2) d to d (3) and e to e (4)

Immunization may sometimes modify the dose response curve by either one of these formulas or in other instances by some of them in the mixed mode Furthermore, the extent to which the formulas are simultaneously relevant may vary in every case Assuming that one of these four formulas interprets the main mode of the modification the data obtained in the present experiments seem to be in accordance with formula (2) or formula (2)

In the present series of experiments the homograft immunization may be considered stronger than against autologous tumors Cellular factors could be neglected since the assay of the Ehrlich cell kinetics in vivo could be undertaken with the diffusion chamber

SUIT & SHALEK (1963) have suggested that an estimated 37 % dose D_o would be smaller than the true D_o of a tumor cell line In this case the tumor cells were cultured in the syngenic hosts to the tumor which had been repeatedly injected with the killed tumor cells In this case the experimental system consisted of a spontaneous mammary adenocarcinoma and syngenic hosts in which weak immunization might exist were adopted cellular factors being included This data may be related to formula (1)

HADDOW (1964) has reported that the effect of a tumor specific immunization for suppressing the increase of the syngenic tumor volume was observed only in the irradiated group of tumors but not in the non irradiated control

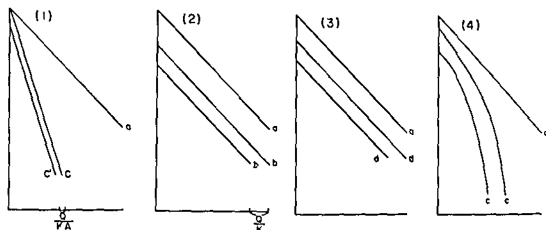


Fig. 10. Further modified theoretical formulas and their curves. These further modified curves were obtained with parallel shift from the right to the left side on semilog section paper.

(1) (a) $N = N_0 e^{-k A_{imm} D}$ where $A_{imm} = 1$

(c) $N = N_0 e^{-k A_{imm} D}$ where $A_{imm} = 3$

(c') $N = N_0 e^{-k A_{imm} D}$ where $A_{imm} = 3$
$D \cong D + Q/k A_{imm}$

(2) (a) $N = N_0 B_{imm} e^{-kD}$ where $B_{imm} = 1$

(b) $N = N_0 B_{imm} e^{-kD}$ where $B_{imm} = 0.5$

(b') $N = N_0 B_{imm} e^{-kD}$ where $B_{imm} = 0.5$
$D \cong D + Q/k$

(3) (a) $N = (N_0 - N_{imm}) e^{-kD}$ where $N_{imm} = 0$

(d) $N = (N_0 - N_{imm}) e^{-kD}$ where $N_{imm} = 0.4 N_0$

(d') $N = (N_0 - N_{imm}) e^{-kD}$ where $N_{imm} = 0.4 N_0$
$D \cong D + Q/k$

(4) (a) $N = N_0 e^{-kD} - N_{imm}$ where $N_{imm} = 0$

(c) $N = N_0 e^{-kD} - N_{imm}$ where $N_{imm} = 0.2 N_0$

(c') $N = N_0 e^{-kD} - N_{imm}$ where $N_{imm} = 0.2 N_0$
$D \cong D + Q/k$

growth, in spite of the fact that N_{imm} had to be $5 \times 10^4 \times (1-0.13)$, i.e. 4.4×10^4 in the present experimental system.

However, the control growth in the immunized hosts did not show a sharp initial drop but rather non significant changes in the cell numbers during the in vivo culture period, especially after 4 days, and the cytolysis experiment in vitro using the iso antiserum mainly suggested an apparent suppression of cell proliferation. Therefore, these four theoretical formulas should be further

crease in cell number is delayed or the growth rate decreases On the other hand in the immunologically treated cells, the morphologic disorder is mainly observed in the cytoplasmic portion which is followed by morphologic desolation in the cell nuclei portion

Thus the two different procedures both irradiation and immunization may co operate to damage the cells by attacking different portions in each cell the effects of which may appear in different manner and be mutually multiplied independently or even synergetically The dose response curve in the in vivo experiment with immunized hosts manifested on semilog section paper an approximately parallel downward shift from that of conventional hosts which means multiplication of the damage by the two procedures However, further damage such as the so-called sensitization effect to irradiation by immunization was not observed The sensitization effect should be further investigated in vitro by adopting the diluted concentration of antibody (around 0 01 volume per cent)

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SUMMARY

Iso-immune ascitic fluid was found to suppress Ehrlich cell growth in a diffusion chamber in vivo The dose response curve in immunized hosts was displaced downwards to be parallel to that of conventional hosts Application of the iso-immune serum against the Ehrlich cells resulted in their cytolysis when incubated in vitro with a complement solution The possibility of the immunolog c aspects contributing to the radiobiologic aspects of carcinoma therapy is d scussed

ZUSAMMENFASSUNG

Es konnte g zeigt werden dass iso-immune Ascitesflussigkeit das Wachstum von Ehrlich zellen in einer D ffusionskammer unterdruckt In immunis erten Individuen war die dosisbedingte Reakt onskurve herabgedruckt und verlief parallel zu der von nicht immunisierten Indiv d en Die Verabreichung von iso-immunem Serum, gegen die Ehrlichzellen fuhrte zu deren Cytolyse wenn s e in vitro mit Komplementflussigkeit inkubiert wurden Es besteht demnach d e Mogl chkeit dass immunologishe Faktoren zu den rad obiologischen Wirkungen d r Kr bsbestrahlung beitragen

group The dose response curve was not shown but formulas (1) or (4) would probably explain this data Formula (4) gives the most theoretically effective inactivation curve for the purpose of cancer therapy In any case in which a weak immunization exists, formulas (1) or (4) may not easily be distinguished by their dose response curves when some sensitization by the immunization occurs

Experimental systems used by HADDOW and SUIT may include the cellular factors in the immunologic reactions, and the data suggest that formula (1) or (4) should be selected On the other hand, in the present experimental system the cellular factors were excluded but the humoral factors were included and formula (2) was suggested It is therefore probable that the humoral factor and the cellular factor in the immunologic reactions modify the dose response relationship in different manners

Cellular aspect of radiation therapy in relation to immunology of cancer The immunology of cancer has passed through three distinct periods as stressed by PREHN (1963) In the first of these, it was demonstrated that experimental animals could be immunized against the growth of transplanted tumors In the second, it was clarified that the previous demonstration had been mainly due to homograft immunity Finally, in the third it was demonstrated that in some isologously transplanted tumors, the growth could be suppressed in the immunized isologous hosts Further, since the tumor specific antigenisities in some human malignancies have been recognized (KLEIN et coll 1966), cancer immunology has become one of the most important aspects of human cancer therapy (CINADER 1963) After changes in cell character have taken place, both autonomous growth and tumor specific antigenisity may be possessed by some of the malignancies If these two processes can exist simultaneously, all such malignancies may possess the tumor specific antigenisity, and if they can exist independently, some of the malignancies may theoretically possess the tumor specific antigenisity whereas others may not (BURCH 1963) The immunization may in the course of tumor therapy cause added damage to a tumor associated with the tumor specific antigenisity Accordingly, in such cases the immunization may modify the dose response relationship, as stressed by SCOTT (1961)

Probably, some of the dose response relationships investigated in vivo and reported upon may have been modified by weak immunization, even if no immunological procedure was employed

Morphological disorder in the irradiated cells is probably observed in the cell nuclei portion primary to morphologic desolation in the cytoplasmic portion Giant cells associated with evident cytoplasm may appear, and in

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RÉSUMÉ

L auteur a constaté que le liquide d ascite iso immun supprime la croissance des cellules d Ehrlich dans une chambre à diffusion in vivo La courbe de réponse en fonction de la dose chez les hotes immunisés est déplacée vers le bas et située parallèlement a celle des hotes non immunisés L incubation in vitro de cellules d Ehrlich avec une solution de complément et application de sérum iso immun entraine leur cytolyse L auteur examine la possibilité d une coopération de l immunologie et de la radiobiologie au traitement du cancer

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expression for it this expression is required for treatment planning with the use of computers

Measurement method The measurements were made with the Gammatron 1 cobalt 60 unit at the Radiotherapy Clinic the unit is equipped with block diaphragms

A Simplex Universal Dosimeter was employed for determination of the doses The radiation was detected with a normal ionization chamber made by the same manufacturer The chamber was encased in perspex to achieve electron equilibrium

Measurements were effected in a water phantom measuring 42 cm × 36 cm × 52 cm with perspex walls Cork material of density 0 27 g/cm³ was utilized as pulmonary tissue equivalent material Flat pieces of the cork material 0 3 to 0 6 cm thick, were placed in a thin walled perspex holder, and a lung phantom was thus obtained The phantom could be changed in position for measurement of the tissue effect at different locations The ionization chamber was situated in one of the pieces of cork By re arrangement of the pieces the position of the chamber could be changed for measurements at different depths in the cork material Four thicknesses of the lung phantom were used 3 1 6 3 9 4 and 12 5 cm the SSD (source to skin distance) was 50 cm

Results of measurements

The maximum dose in cobalt teletherapy is obtained at 0 5 cm below the surface this is assigned as the 100 % dose All other doses are compared with the maximum dose and are termed per cent depth doses

The central axis depth dose curve Straight lines are obtained when the logarithms of the per cent depth doses are plotted as functions of the depth below the surface (JONES et coll 1956 PFALZNER 1960) STERLING et coll (1964) have shown the possibility of expressing the per cent depth doses at the central axis as a function of the area per perimeter of the field According to their findings the following formula is valid

$$\log C_t = h_t + m_t \log (A/P) \qquad (1)$$

where C_t is the per cent depth dose on the central axis of the field at a distance D_t (cm) from the surface

A/P is the ratio of the field area (cm²) over field perimeter (cm)

h_t and m_t are the intercept and slope constants respectively

FROM THE RADIOTHERAPY CLINIC (PROF S MUSTAKALLIO), UNIVERSITY CENTRAL HOSPITAL, HELSINKI, FINLAND

EMPIRICAL FORMULAS FOR TISSUE CORRECTION FACTORS IN COBALT TELETHERAPY

by

ERIK SPRING and PENTTI ANTTILA

Air filled lung tissue has an absorbing capacity which is considerably lower than that of the other soft tissues of the thorax Consequently, any change in the radiation scattering conditions will greatly affect the dose distribution The dose in the lung and behind it increases This is important for the treatment planning, when such influence to the greatest extent possible must be taken into account

Dose distributions are usually determined in a tissue equivalent medium, generally water The change in distribution within and behind an inhomogeneity is observed and given due consideration in the treatment planning by means of tissue correction factors The dose in the inhomogeneous region is arrived at by multiplication of the dose obtained in a homogeneous medium with the correction factor

Tissue correction factors may be determined in several ways One way is to compare the incident and exit doses determined for a patient with measurements performed with a tissue equivalent phantom (PFALZNER 1958, JOHNS 1964) Measurements effected in a tissue equivalent phantom (BURLIN 1957, DAHL and VIKTERLOF 1960, SUNDBOM 1965) or in the oesophagus (VOUTILAINEN & VAHATALO 1966) are also used A tissue equivalent phantom has been employed in this study

The aim of this work was to study the influence of pulmonary tissue upon the central axis depth dose curve with a view to finding a simple mathematical

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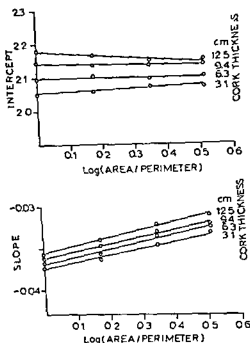


Fig 3 Intercept and slopes of the straight lines adapted to the experimental values measured behind the cork phantom Some of the results are given in figs 4 and 5

dose curve within the lung can approximately be described by one formula If the logarithm of the measured doses as a percentage of the depth dose value in the normal tissue at the boundary of the pulmonary tissue is plotted as a function of $\log(A/P)$ straight lines result The experimental values together with the straight lines are presented in Fig 2 If the slopes and the intercepts of the lines are plotted as functions of the depth in the pulmonary tissue approximately straight lines are obtained The per cent depth dose in the pulmonary tissue may be expressed by the formula

$$C_l = (k_l/100)\, C_a \qquad (3)$$

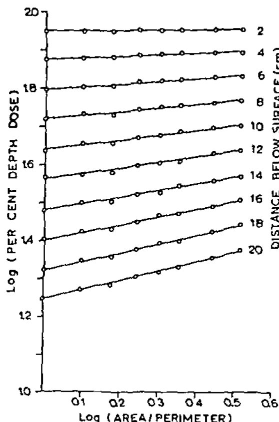
where

C is the normal tissue per cent depth dose at the entrance boundary between the normal tissue and the pulmonary tissue It can be calculated by formula (2)

$k_l = \text{antilog}[-0.024\, D_l + (0.004\, D_l - 0.008)\log(A/P) + 1.980]$

D_l is the depth in the pulmonary tissue measured in cm

Figs 4 and 5 indicate the closeness of fit between the experimental points and the lines obtained by means of formula (3) The depth doses re



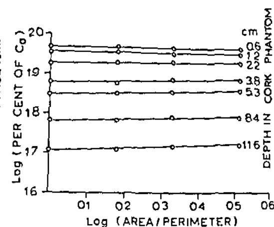


Fig 1 (left) Change in the central axis depth dose as a function of log (area/perimeter) of the field at 50 cm SSD

Fig 2 (above) Change in the central axis depth dose within the pulmonary tissue equivalent cork phantom C_0 denotes the dose in water at the entrance boundary between water and cork

Use has been made of formula (1) in study of the central axis depth dose curve Fig 1 illustrates the results of measurements and the straight lines determined by the method of least squares It is apparent that close agreement exists between the experimental points and the straight lines These provide a basis for determination of the constants h_i and m_i $h_i = -0\,039\ D_i + 2\,033$ and $m_i = 0\,013\ D_i + 0\,006$

Finally, the value of C_i, the per cent depth dose on the central axis at a distance D_i (cm) below the surface, is derived from the formula

$$C_i = \text{antilog}[-0\,039\ D_i + (0\,013\ D_i + 0\,006)\log(A/P) + 2\,033] \qquad (2)$$

This formula describes very well the central axis depth dose curve, as is evident from Figs 4 and 5 An additional check of formula (1) was made by measuring the dose at different depths below the surface and a constant value of (A/P) but by introducing variation in the length of sides of the field The results were found to lie within 1 %

Measurements within the inhomogeneity The measurements in lung equivalent tissue were made with the cork phantom described It was found that the depth

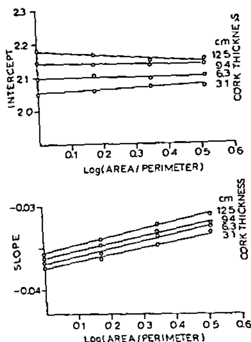


Fig 3 Intercepts and slopes of the straight lines adapted to the experimental values measured behind the cork phantom Some of the results are given in figs 4 and 5

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$$C_t = (k_t/100)\ C_a \qquad (3)$$

where

C_a is the normal tissue per cent depth dose at the entrance boundary between the normal tissue and the pulmonary tissue It can be calculated by formula (2)

$k_t = \text{antilog}[-0.024\ D_t + (0.004\ D_t - 0.008)\log(A/P) + 1.980]$

D_t is the depth in the pulmonary tissue measured in cm

Figs 4 and 5 indicate the closeness of fit between the experimental points and the lines obtained by means of formula (3) The depth doses re

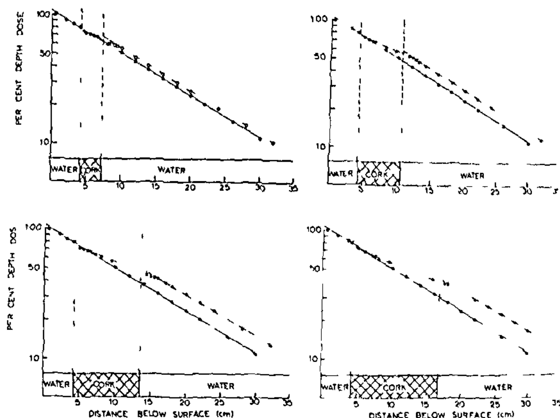


Fig. 4. Experimental results of measurements with SSD = 50 cm, field 13 cm × 13 cm and different thicknesses of the cork phantom (ρ = 0.27 g/cm³).
● measurements in water
ı measurements within and behind the cork phantom
—— calculated by formula (2)
calculated by formula (3) and (4)

remained constant for constant values of (A/P), even within the cork phantom. The deviations in measurement lay within 1 %.

Measurements behind the inhomogeneity. Finally, measurement was made of the depth doses beyond the pulmonary tissue, in the water behind the cork material.

Some of the derived experimental values are reproduced in Figs. 4 and 5. First, by application of the method of least squares, straight lines were adapted to the experimental points, taken as the logarithms of the per cent depth doses. The intercepts and slopes obtained for these lines are given in Fig. 3 as functions of log (A/P). Plotting the intercepts and slopes as functions of the cork thickness will permit the adaptation of straight lines to the points concerned. Thus, formulas are obtained for the calculation of these para-

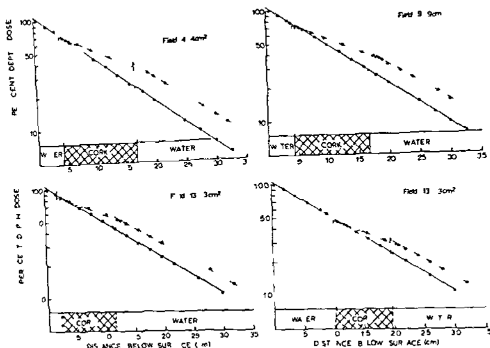


Fig 5 Results similar to those in fig 4 for SSD = 50 cm and fields 4 cm × 4 cm 9 cm × 9 cm and field 13 cm × 13 cm and the cork phantom at two different depths below the surface
● measurements in water
measurements within and behind the cork phantom
—— calculated by formula (2)
calculated by formulas (3) and (4)

meters for different cork thicknesses In all the per cent depth doses behind the pulmonary tissue can be determined with the help of the following formula

$$C_t = \text{antilog}_{10}\{[(0\,0001\, d_t + 0\,0081)\log(A/P) + 0\,0002\, d_t - 0\,0382]D_t + (-0\,0103\, d_t + 0\,0703)\log(A/P) + 0\,0132\, d_t + 2\,0151\} \qquad (4)$$

where C_t is the per cent depth dose at the central axis at a depth D_t (cm) below the skin

d_t (cm) is the thickness of the pulmonary tissue

The other parameters have been defined earlier The calculated results are compared with the experiments in Figs 4 and 5 The depth dose was measured behind the cork material keeping the ratio (A/P) constant and varying the field sides The results obtained were within 1 %

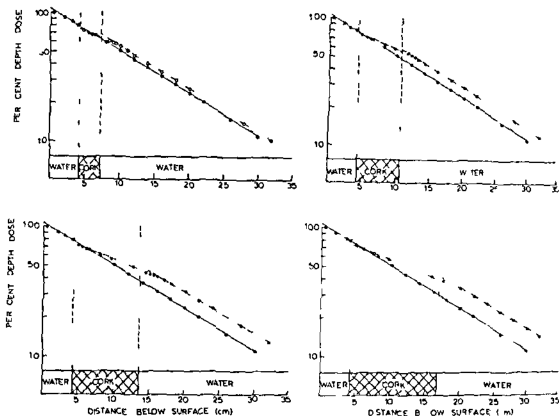


Fig 4 Experimental results of measurements with SSD = 50 cm field 13 cm × 13 cm and different thicknesses of the cork phantom (ρ = 0 27 g/cm³)
● measurements in water
○ measurements within and behind the cork phantom
—— calculated by formula (2)
calculated by formula (3) and (4)

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Acknowledgement

The authors wish to thank Mr S Verho for his assistance in this study

SUMMARY

A study was performed with the aim of finding simple mathematical expressions for the per cent depth doses when pulmonary tissues are included Three formulas are presented that fulfil the requirements for application in treatment planning using computers

ZUSAMMENFASSUNG

Einfache mathematische Formeln um die prozentualen Tiefendosen zu bestimmen wenn die Bestrahlung auch Lungengewebe inkludiert wurden studiert Als Resultat werden drei Formeln presentiert und diese genugen um einen Bestrahlungsplan mit Hilfe einer Datenver arbeitungsmaschine aufzustellen

RÉSUMÉ

Les auteurs ont cherché une expression mathématique simple du pourcentage de dose en profondeur quand le volume irradié comprend du tissue pulmonaire Les résultats obtenus sont presentés sous forme de trois plans de traitement pour ordinateur

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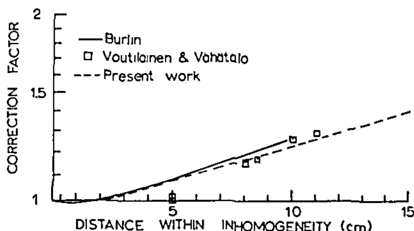


Fig. 6. Experimental results of BURLIN (1957) (SSD 50—70 cm, field 10.7 cm × 10.7 cm, phantom density $\varrho = 0.38$ g/cm³), VOUTILAINEN & VAHÄTALO (1966) (SSD 60 cm, field 64—150 cm², measurements in an oesophagus) and the present study (SSD 50 cm, field 10 cm × 10 cm, $\varrho = 0.27$ g/cm³).

Discussion

It has been demonstrated that the per cent depth dose at the central axis of the beam can be calculated by means of three formulas, if the effect of pulmonary tissue is to be taken into account. The first formula (2) is valid in the front of the lung, the second (3) within it, and the third (4) behind it. Fig. 4 presents the values calculated in comparison with those derived by experiment for different thicknesses of the lung phantom. Fig. 5 contains a few examples of measurements with different field sizes and different positions of the cork phantom. The agreement between the experimental points and the lines calculated theoretically is seen to be rather close. Of course, the values calculated are not valid in the close vicinity of the tissue boundaries.

Interest is attached to a comparison of these results with the correction factors published earlier. A comparison is made in Fig. 6 which reveals that the SSD does not greatly affect the factors, as has previously been pointed out by BURLIN (1957). The correction factor curves published by BURLIN lie slightly above the curve now presented, while the factors reported by VOUTILAINEN & VAHATALO (1966) are slightly smaller than the present ones. Details of measurements are given in Fig. 6.

BURLIN demonstrated that the correction factors reach a constant value about 6 cm behind the inhomogeneity induced by the pulmonary tissue equivalent material. Reference to Figs. 4 and 5 will show that the present results disclose no constant value. The factors increase slowly, even to a depth of about 15 cm, although the increase is so insignificant that the observation made by BURLIN is more or less valid.

Experimental arrangement The experiments were performed with a Siemens Tridoros 5 S diagnostic unit a three phase machine with 12 dry rectifiers The tube a Bi 100/30/50 RM with 0 5 mm Al inherent filtration had a 0 6 mm and 1 mm double focus A suitable field size and adequate limitation of the beam was obtained by means of a long cylinder the focus-film distance was 80 cm Ferrania industrial film fine grain without intensifying screens was used

The breast phantom was manufactured by the Minnesota Mining and Manufacturing Company and consisted of transparent non granular plastic with an effective atomic number of 6 41 and density 1 14 It had the same response to roentgen radiation as a human subject Several objects were embedded on a horizontal plane in the middle of the phantom and included five sections of stainless steel wire placed parallel to one another and measuring 1 mm 0 5 mm 0 25 mm 0 125 mm and 0 05 mm in diameter as well as gelatine capsules of air and bone dust and a section of human bone with the cancellous structure visible

Effect of the filters upon 30 kV —35 kV roentgen radiation It is an established fact that a Fe filter due to its higher atomic weight will have a greater effect upon the softer part of the roentgen spectrum than an Al filter The absorption in the Fe filter of photons of this energy is only of a photo-electric nature The energy of the K radiation from iron is about 8 keV and at a distance of 80 cm this will be practically absorbed in the air Thus the unnecessary soft radiation to the skin can be reduced in comparison with the use of only the inherent Al filter

Results

The films were exposed to the same blackening measured by means of a Macbeth Ansco densitometer The image qualities were examined by means of the different objects embedded in the middle of the breast phantom

The skin exposure per film with different filters and kilovoltages was as follows

kV	Filters	Skin exposure/Film
30	0 5 Al	24 5 R
35	0 5 Al + 0 038 Fe	8 9 R
35	0 5 Al + 0 050 Fe	4 2 R

The relative low skin exposures at 35 kV were not due to the filtration alone since the film sensitivity is somewhat greater at 35 kV than at 30 kV

In examinations of patients with 30 kV and a 0 5 Al filter the average value of skin doses per film was about 10 R This means that the dose to patients may

FROM STATENS INSTITUTT FOR STRÅLEHYGIENE, OSLO, NORWAY

IRON FILTERS AS A MEANS OF REDUCING THE DOSE IN ROENTGEN EXAMINATION OF THE FEMALE BREAST

by

Sem Maudal

Attention has long been directed to filters as being the best means of obtaining the most useful quality of roentgen radiation. Thoraeus developed multifilter combinations of tin, copper and aluminium to avoid too much soft radiation in deep therapy. These filters, compared to those of pure copper, are particularly efficient around 250 kV and 300 kV. Trout, Kelley & Cathey performed a series of measurements with different aluminium filters in the range between 50 to 130 kV for the purpose of establishing a means of reducing the exposure to the patient in roentgen diagnosis. The work of Bosche & Frik in this field must also be mentioned: these authors reported the advantages of iron over copper filters in the 60 to 150 kV roentgen radiation range.

Roentgen examination of the female breast is relatively new. The most useful quality of roentgen radiation has been found to lie in the range between 20 kV and 40 kV; the technique has been fully described by Egan.

The aim of the present investigation was to determine the influence of different iron filters upon the optimal image quality in relation to the radiation dose to the patient.

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Experimental arrangement. The experiments were performed with a Siemens Tridoros 5 S diagnostic unit, a three phase machine with 12 dry rectifiers. The tube, a Bi 100/30/50 RM with 0.5 mm Al inherent filtration, had a 0.6 mm and 1 mm double focus. A suitable field size and adequate limitation of the beam was obtained by means of a long cylinder; the focus-film distance was 80 cm. Ferrania industrial film, fine grain, without intensifying screens, was used.

The breast phantom was manufactured by the Minnesota Mining and Manufacturing Company and consisted of transparent non-granular plastic with an effective atomic number of 6.41 and density 1.14. It had the same response to roentgen radiation as a human subject. Several objects were embedded on a horizontal plane in the middle of the phantom and included five sections of stainless steel wire placed parallel to one another and measuring 1 mm, 0.5 mm, 0.25 mm, 0.125 mm and 0.05 mm in diameter, as well as gelatine capsules of air and bone dust, and a section of human bone with the cancellous structure visible.

Effect of the filters upon 30 kV—35 kV roentgen radiation. It is an established fact that a Fe filter, due to its higher atomic weight, will have a greater effect upon the softer part of the roentgen spectrum than an Al filter. The absorption in the Fe filter of photons of this energy is only of a photo-electric nature. The energy of the K radiation from iron is about 8 keV and at a distance of 80 cm this will be practically absorbed in the air. Thus the unnecessary soft radiation to the skin can be reduced in comparison with the use of only the inherent Al filter.

Results

The films were exposed to the same blackening, measured by means of a Macbeth Ansco densitometer. The image qualities were examined by means of the different objects embedded in the middle of the breast phantom.

The skin exposure per film with different filters and kilovoltages was as follows:

kV	Filter	Skin exposure/Film
30	0.5 Al	24.5 R
35	0.5 Al + 0.038 Fe	8.9 R
35	0.5 Al + 0.050 Fe	4.2 R

The relative low skin exposures at 35 kV were not due to the filtration alone since the film sensitivity is somewhat greater at 35 kV than at 30 kV.

In examinations of patients with 30 kV and a 0.5 Al filter the average value of skin doses per film was about 10 R. This means that the dose to patients may

be expected to be only half of the values obtained with the phantom. These results suggest that roentgen examination of the female breast may be performed with about 2 R per exposure.

We found after completion of our investigation that HRANITZKY & SHALEK had published a study in which aluminium filters had been added and in which the skin doses were found to vary between 2 and 23 rad per film.

Acknowledgement

The author wishes to thank K. Liverud for placing the mammography laboratory at his disposal for the present investigation.

SUMMARY

Measurement of skin exposures in roentgen examinations of the female breast demonstrated that with the use of iron filters the examinations can be performed with about 2 R per exposure.

ZUSAMMENFASSUNG

Für die Röntgenuntersuchung der weiblichen Brustdrüse wurde der Einfluss von Eisenfiltern auf die Hautbelastung erforscht und es wurde gezeigt, dass ungefähr 2 R per Exponierung genügen.

RÉSUMÉ

Des mesures de dose à la peau ont montré l'effet de filtres de fer pour l'examen radiographique du sein chez la femme. L'examen peut être fait avec environ 2 R par film.

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ASPIRATION BIOPSY IN DIAGNOSIS OF PALPABLE LESIONS OF THE BREAST

Critical review of 3 479 consecutive biopsies

by

S Franzen and J Zajicek

The value of aspiration biopsy in the diagnosis of mammary carcinoma has been much discussed in the literature (Stewart 1933 Martin & Stewart 1936 Sayago 1942 Adair 1949 Budd 1949 Piaggio Blanco & Paseyro 1950 Saphir 1952 Dustin Jr 1953 Johnston Jr 1954 Cornillot & Verhaeghe 1955 1959 Fleming 1955 Rosemond et coll 1955 Temime 1956 Gibson & Smith 1957 di Paola et coll 1957 Tailhefer 1957 Bethel 1958 Godwin 1958 Blaudin de Thé 1959 Smith et coll 1959 Viaggio & Eguia 1959 Marsan & Bertini 1960 Shiller Volkova & Agamova 1960 Berg 1961 Glassman 1961 Klimanova 1961 Dargent 1962 Rosemond 1963 Verhaeghe 1963 Zajdela 1963 Soderstrom 1966 Zajicek et coll 1967) Opinions on the method range from almost total rejection to enthusiastic acceptance

Aspiration biopsy is however in certain circumstances generally accepted as the diagnostic method of choice It is commonly agreed that in inoperable carcinoma of the breast needle aspiration is preferable to surgical biopsy for confirming the

From Radiumhemmet and the Department of Clinical Cytology the Institute of Radiopathology Karolinska Sjukhuset Stockholm Sweden Submitted for publication 29 February 1968

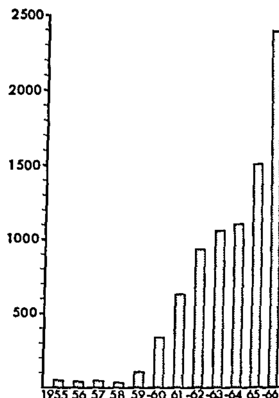


Fig 1 Frequency of aspiration biopsy in mammary tumour diagnoses at Radiumhemmet 1955—1966

diagnosis prior to radiotherapy For distinguishing between diffuse suppurative mastitis and carcinoma accompanied by severe inflammation, aspiration biopsy likewise is widely preferred

The indications for aspiration biopsy in other cases may vary from clinic to clinic In some centres its use may be confined to evacuation of cysts The procedure is then therapeutic, but it may eliminate the need for surgery if the palpatory findings become normal after removal of the cystic contents Other clinicians use aspiration biopsy of the breast mainly on suspicion of malignant but potentially operable lesions a positive cytologic report is then followed by radical mastectomy without prior recourse to surgical biopsy

At Radiumhemmet aspiration biopsy is done on all palpable lesions of the breast Thus, it is used to establish the diagnosis before radiotherapy in presumed cancer for which surgery is judged to be contra indicated When surgery is intended, regardless of the result of the cytologic examination, aspiration biopsy is done to assist in planning its extent excisional biopsy for cytologically benign or only possibly malignant lesions, and radical mastectomy when the cytologic report states carcinoma

To investigate the usefulness of needle biopsy for revealing carcinoma of the

breast when such a wide range of indications for the procedure is used 3 479 consecutive aspiration biopsies performed at Radiumhemmet were reviewed, and the cytologic reports were compared with clinical and histologic findings The results are now presented and the advantages and limitations of this cytologic method in the detection of mammary carcinoma in palpable lesions are discussed

Clinical material The frequency of aspiration biopsy of the female breast at Radiumhemmet between 1955 and 1966 is recorded in Fig 1

The present study covers the years 1955—1963 During this period aspiration biopsy of the breast was performed on 3 479 occasions in 3 023 women who attended Radiumhemmet because of a palpable mass in mammary tissue Of these women 86 were excluded from the present study because the aspiration biopsies were performed after surgery or radiotherapy or because surgery was delayed until six months or more after aspiration biopsy

The conclusions concerning the diagnostic accuracy of aspiration biopsy are based on 2 937 women 1 686 of whom were subsequently operated on In 27 women aspiration biopsy and subsequent surgery involved both breasts each breast is then considered as a separate case When aspiration biopsy was done more than once before operation only the cytologic findings from the first biopsy are reported

Aspiration of 1 406 breasts in 1 251 women was not followed by surgery In these cases the cytologic and clinical findings are compared Again each breast is reported as a separate case and only the first needle biopsy is considered

Technique of aspiration biopsy A Luer Lok syringe with a special handle which permits a single hand grip was used (FRANZEN et coll 1960 ZAJICEK et coll 1967) Disposable 0 6 mm needles are usually satisfactory such a fine needle minimizes admixture of blood but a thicker needle may occasionally have to be substituted if the initial attempt indicates presence of dense fibrotic tissue e g in the wall of a mammary cyst

No anaesthesia is given The skin is wiped with antiseptic solution and the mass is grasped with one hand in a position favourable for needling Superficially sited lesions are held between the index finger and thumb and are punctured with a short (about 3 cm) needle Longer needles (about 6 cm or more) are used for deeper seated lesions in voluminous breasts

The needle having entered the tumour area the plunger of the syringe is retracted so that a vacuum is created in the system while the needle is guided in a straight line through the lesion In order to obtain sufficient material particularly from fibrotic lesions the needle may have to be moved back and forth in

the mass up to five times and possibly inserted into different areas of the mass Throughout this manipulation, negative pressure is maintained in the syringe by keeping the plunger retracted When the aspiration has been completed, the *pressure in the syringe is allowed to equalize* before the needle is withdrawn from the tumour It is important that no pressure difference remains in the system when the needle is withdrawn for otherwise tumour cells may be aspirated into the needle track The syringe is disconnected from the needle, filled with air and reconnected The contents of the needle are then carefully expressed on to a glass slide

Preparation of the smear The aspirate is spread along the slide Aspirate which contains blood or cystic fluid must be spread with the aid of a thick coverslip (such as used in a Burker counting chamber) as for an ordinary blood smear Any largish tissue fragments that collect at the end of the smear are gently squeezed by flat pressure with the coverslip used to spread the smear If the aspirate consists of greyish, solid or semisolid material, the smear is best prepared *by firm, flat pressure with the coverslip*

The fluid aspirated from cysts was discarded if it was transparent and no residual mass could be palpated If, however, the aspirate was turbid or haemorrhagic, or if a palpable swelling persisted after the aspiration, the cystic contents were cytologically analyzed A few drops of heparin were added to prevent clotting of haemorrhagic aspirate

Fixing and staining of smears Methods of fixing and staining smears of biopsy aspirate have excited some controversy In some collaborative reports from clinicians and pathologists, wet fixation and stains such as Papanicolaou or haematoxylin eosin have been recommended in order to give maximum resemblance between the aspirated cells and their equivalents in tissue sections One disadvantage of this method is that the aspirates dry fairly quickly, which makes for variability in fixing and staining BERG (1961), however, accepted air drying of the smears, and use of the mentioned stains though these were originally devised for wet fixed smears or tissue section He pointed out that the sine qua non of *microscopic diagnosis is the recognition of a repeated pattern* and considered the loss of microscopic detail to be compensated for by consistency in the preparation of large numbers of smears

Haematologic experience also indicates air drying as the method of choice, but this with stains initially intended for air dried smears of blood or bone marrow The May Grunwald Giemsa (MGG) stain is used as a standard by most haematologists

Smears at Radiumhemmet are usually dried in air and stained with MGG

Whenever possible additional smears are prepared from the same specimen by immediate fixation in equal parts of ethyl alcohol and ether and stained according to Papanicolaou This practice was introduced in order to collect material for comparison of the diagnostic merits of the two methods

The success of the MGG stain in haematology is mainly due to its quality of disclosing cytoplasmic details such as degrees of basophilia and granulation It stains both nuclei and cytoplasm intensively and analysis therefore requires a monolayer cell distribution This implies that MGG staining of needle aspirate is best suited for tissues such as lymph nodes and bone marrow since the yield then is mainly individual cells which can be spread in a single layer In malignant tumours the intercellular cohesion usually is greatly reduced (COMAN 1944), and therefore aspirate from such tumours is likewise well suited for staining with MGG When the aspirate derives from benign tumours such as fibroadenoma and consists of large plugs of overlapping cells wet fixation and more selective staining of the nuclei e g with Harris haematoxylin may be preferable Wet fixation may also be better when the aspirate is necrotic or if there is cytoplasmic degeneration for instance in material from cystic lesions

The decision for or against supplementing air dried mears with wet fixed smears may be made from case to case when the first slide has been spread with aspirate and macroscopically evaluated

Cytologic and histologic examinations All the aspiration biopsies were performed by cytologists at Radiumhemmet and in the individual cases the cytologist who read the slides had usually also performed the biopsy Only the diagnoses made at the original reading of the slides are tabulated When present opinion differs from the original diagnosis this is discussed in the text

The histologic diagnoses were made in the pathology departments of the various hospitals to which the patients were referred for surgery In the cases operated on at Karolinska Sjukhuset (about 40 per cent of the total series) the diagnoses were made at the Institute of Radiopathology The original histologic diagnoses are used in the comparative study Current opinion in cases with an initial histologic diagnosis of precancerous lesion is discussed separately on page 14

Results

Series A — Aspiration biopsy findings in 1 713 breasts with subsequent histologic diagnosis

The cytologic reports on the 556 breasts (546 women) with a histologic diagnosis of benign non neoplastic conditions are presented in Table 1

In 19 of the 41 cases of mastitis the aspiration biopsy smears had revealed

Table 1

Cytologic findings in 556 breasts with subsequent histological diagnosis of non neoplastic disorders — Figures in parentheses indicate percentages

Cytologic findings	Histologic diagnoses				Total
	Mastitis	Fat necrosis	Fibrocystic mastopathy	Fibrosing adenosis	
Fat blood or no yield	4 (9 8)	1 (16 7)	63 (12 8)	—	68
Cystic fluid	10 (24 4)	—	199 (40 4)	1 (6 2)	210
Inflammatory cells	19 (46 3)	5 (83 3)	8 (1 6)	—	32
Benign epithelium	7 (17 1)	—	171 (34 7)	9 (56 3)	187
Fibroadenoma	—	—	9 (1 8)	3 (18 8)	12
Cellular atypia	1 (2 4)	—	32 (6 5)	2 (12 5)	35
Carcinoma suspected	—	—	10 (2 0)	1 (6 2)	11
Carcinoma	—	—	1 (0 2)	—	1
Total	41	6	493	16	556

inflammatory cells, such as granulocytes, lymphocytes and histiocytes Inflammatory cells were also present in five of the 6 cases of fat necrosis, along with degenerated fat cells and or lipophages

Fibrocystic disease was the histologic diagnosis in 493 breasts The aspirate was reported to be cystic fluid in 199 of these, and benign epithelium in 171 In 9 cases of fibrocystic disease the cytologic examination suggested fibroadenoma Cellular atypia was reported in 32 cases of the same group and carcinoma was cytologically suspected in 10 cases A cytologic diagnosis of carcinoma was made in one case (Fig 2a), which is discussed later

Fibrosing adenosis was found at histologic examination in 16 cases, in nine of which the cytologic report was benign epithelium and in one case cystic contents Three cases were cytologically regarded as fibroadenomas Cellular atypia was reported in two cases and carcinoma was suspected in the remaining case

Table 2 concerns the 251 breasts (249 women) in which the histologic examination disclosed benign tumours In the single case of haemangioma aspiration biopsy yielded only blood The aspirate from 12 of the 15 lipomas consisted chiefly of fat The cytologic report had suggested lipoma in most of these cases this was partly based on palpation of freely mobile, fairly well defined swellings that were clinically considered to be cysts, adenomas or lipomas Intraductal papilloma was histologically diagnosed in 11 cases, in six of which the preceding aspiration biopsy had yielded epithelium of benign appearance and in five no material or only cystic fluid

Table 2

Cytologic findings in 251 breasts with subsequent histologic diagnosis of benign tumour — Figures in parentheses indicate percentages

Cytologic findings	Histologic diagnoses				Total
	Haemangioma	Lipoma	Intraductal papilloma	Fibroadenoma*	
Fat blood or no yield	1	12 (80)	3 (27 3)	12 (5 4)	28
Cystic fluid	—	—	2 (18 2)	3 (1 3)	5
Inflammatory cells	—	—	—	2 (0 9)	2
Benign epithelium	—	3 (20)	6 (54 5)	66 (29 5)	75
Fibroadenoma	—	—	—	129 (57 6)	129
Cellular atypia	—	—	—	—	—
Carcinoma suspected	—	—	—	12 (5 3)	12
Total	1	15	11	224	251

* In 4 cases the histologic report also stated suspected cystosarcoma phyllodes

Fibroadenoma was the histologic diagnosis in 224 cases though the reports in four of these cases suggested possible cystosarcoma phyllodes Table 2 reveals that in 129 (57 6 per cent) of this group, fibroadenoma had already been reported in the cytologic examination In twelve cases there was cytologic suspicion of malignancy No false positive diagnosis of carcinoma was made

The cases of precancerous lesion and of mammary carcinoma are presented in Table 3 which also summarizes Tables 1 and 2 As already stated the cytologic reports suggested malignancy in 23 of the 807 cases with histologically benign mastopathies The single case in which a clear cytologic diagnosis of malignancy was followed by a histologic report of a benign condition is discussed later

Precancerous lesions were histologically observed in 33 cases Table 3 indicates that in four of these cases the cytologic report stated carcinoma and in four other cases suspected carcinoma After a recent review of the histologic slides 20 of the thirty three cases were reclassified according to modern nomenclature as intraductal carcinoma The implications of this reclassification as regards the cytologic diagnosis are treated in the discussion

Invasive carcinoma was present (or in six cases suspected) at histologic examination in 873 breasts (858 women) In 77 (8 8 per cent) of these histologically diagnosed carcinomas the cytologic examination did not indicate malignancy and in 17 cases (1 9 per cent) only cellular atypia was reported Malignancy was suggested by the cytologic examination in 117 cases (13 4 per cent),

Table 3

Cytologic findings in 1 713 breasts with subsequent histologic diagnosis of benign lesion of precancerous lesion or carcinoma — Figures in parentheses indicate percentages

Cytologic findings	Histologic diagnoses			Total
	Benign lesion*	Precancerous lesion including intraductal carcinoma	Carcinoma**	
Fat blood or no yield	96 (11 9)	1 (3 0)	29 (3 3)	126
Cystic fluid	215 (26 6)	7 (21 2)	6 (0 7)	228
Inflammatory cells	34 (4 2)	—	—	34
Benign epithelium	262 (32 5)	13 (39 4)	39 (4 5)	314
Fibroadenoma	141 (17 5)	3 (9 1)	3 (0 3)	147
Cellular atypia	35 (4 3)	1 (3 0)	17 (1 9)	53
Carcinoma suspected	23 (2 9)	4 (12 1)	117 (13 4)	144
Carcinoma	1 (0 1)	4 (12 1)	662 (75 8)	667
Total	807	33	873	1 713

* In 4 cases the histologic report stated suspected cystosarcoma phyllodes

** In 6 cases the histologic report was suspected invasive carcinoma

but the evidence was considered to be insufficient to warrant a definite recommendation of radical surgery In the remaining 662 cases (75 8 per cent) the cytologic report stated malignancy and advised radical operation

Series B - Aspiration findings in 1 406 breasts without histologic diagnosis

The cytologic reports and the clinical findings in the breasts in which aspiration biopsy was not followed by surgery are presented in Table 4 It is seen that 37 cases were clinically classified as simple mastitis, and that cytologic confirmation of this diagnosis was obtained in 26 cases In 340 of the 583 breasts with fibrocystic disease, aspiration biopsy yielded benign epithelial cells Large solitary cysts were clinically considered to be present in 139 cases in 96 of which aspiration biopsy yielded cystic fluid

The clinical diagnosis in 214 cases was simply tumour without further specification The cytologic examination in 98 of these cases indicated that the tumour was a large cyst In the 120 cases clinically described as benign adenoma, the most common cytologic diagnoses were cyst (40 cases) and fibroadenoma (29 cases)

Table 4

Cytologic and clinical findings in 1 406 breasts without histologic diagnosis

Cytologic findings	Clinical findings							Total
	Mastitis	Fibro-cystic disease	Cyst	Tumour	Adenoma	Carcinoma suspected	Carcinoma	
Fat blood or no yield	3	118	5	74	13	23	3	239
Cystic fluid	5	77	96	98	40	19	20	355
Inflammatory cells	26	22	1	25	4	4	3	85
Benign epithelium	2	340	20	—	32	39	1	434
Fibroadenoma	1	16	15	16	29	—	—	77
Cellular atypia	—	10	2	1	2	1	—	16
Carcinoma (suspected)	—	—	—	—	—	—	24	24
Carcinoma	—	—	—	—	—	1	175	176
Total	37	583	139	214	120	87	226	1 406

Carcinoma was clinically considered likely in 87 cases In 43 of them carcinoma had previously been found in the other breast The cytologic report stated carcinoma in only one of these 87 cases

Carcinoma was clinically considered to be present in 226 cases and was cytologically confirmed in 175 cases (77 4 per cent) In a further 24 cases (10 6 per cent) malignancy was cytologically suspected Thus in 27 cases (11 9 per cent) the aspiration biopsy smears were negative for carcinoma and in twenty of these cases the aspirate consisted predominantly of cystic fluid Poor general health or refusal of permission to operate were the reasons why surgical biopsy and thereby histologic examination were not done in this group of cases

Discussion

At Radiumhemmet aspiration biopsy of palpable lesions of the breast and other organs is performed by cytologists and as a rule the cytologist who analyzes the smears prepared from the aspirate has also done the biopsy He therefore has the advantage of direct confrontation with the clinical problem and can form his own opinion of the case He can also collect additional information

while needling the lesion and preparing the smear, during the needling he will learn more about the size, site and consistency of the mass The consistency — soft, solid or fibrotic — may have implications regarding the cellularity of the aspirate The presence of capsular tissue may occasionally be apprehended, for example in some cases of lipoma, fibroadenoma or cyst

Naked eye inspection of the aspirate may also be helpful Indeed, it is essential to assess the adequacy of the sample, and consequently whether or not the biopsy should be repeated The aspirate from mammary lesions may be fluid, semisolid or solid, possibly with admixture of blood Fluid aspirate suggests that a cyst is present and this should prompt the examiner to re appraise the lesion after the aspiration If any residual mass can then be palpated, a second aspiration should be done Inspection of solid aspirate may likewise be rewarding When spreading solid aspirate, the experienced examiner can make a fairly accurate macroscopic judgement of whether it contains plugs of tumour tissue or consists predominantly of necrotic or amorphous material Findings of the latter types should lead to repetition of the biopsy, possibly from the periphery of the mass from where well preserved cell populations may be more easily aspirated

At this stage the examining cytologist may also decide if he will prepare both air dried smears and wet fixed smears, the latter to be stained according to Papanicolaou or with other, more specific stains used in modern cytochemistry If a circumscribed mass yields transparent material, which when spread on a glass slide resembles fat, lipoma can be considered as the diagnosis But should the examiner be uncertain if such aspirate has been sampled from within the mass, the biopsy should be repeated since the cytologic report of lipoma will stand or fall on that judgement

Consequently, the cytologic diagnosis of mammary lesions is based on a summation of the clinical assessment prior to aspiration biopsy, the observations made during needling of the mass, and the microscopic evaluation of the slides The foregoing remarks further indicate that optimal conditions for diagnostic work with aspiration biopsy are obtained when the same cytologist observes the clinical features of the case during the biopsy and can personally handle the fragile aspirated material when spreading it on the slides At present such optimal conditions exist in certain centres, such as Radiumhemmet in Stockholm, Fondation Curie in Paris (ZAJDELA 1967) and Centre Oscar Lambret in Lille (CORNILLOT 1967), France When slides of aspirate are delivered to the cytologist *from other* departments or hospitals, much depends upon the amount and relevance of the written information and even more on the skill with which this material has been obtained and the slides have been prepared If the clinical information is inadequate and the slides are not representative or are badly prepared, the diagnostic results will be poor (SODERSTROM 1966, p 153)

The main purpose of the present paper has been to evaluate the usefulness of fine needle biopsy in the diagnosis of mammary carcinoma In the following we shall also briefly deal with other common disorders of the breast such as simple mastitis cystic mastopathy fibrosing adenosis and fibroadenoma The discussion will be confined to cases in which aspiration biopsy was followed by surgery and histologic diagnoses therefore were available for comparison i e the cases listed in Tables 1 2 and 3

Mastitis The aspirate in diffuse suppurative mastitis most commonly consists of fluid semisolid or solid material containing numerous inflammatory cells such as granulocytes lymphocytes monocytes foam cells and phagocytes The diagnosis can then be readily made Sometimes however, large sheets of foam cells and of histiocytes with enlarged nuclei present problems for the inexperienced examiner (Fig 2, b and c) But careful analysis of the general appearance of the smear should clearly reveal the benign nature of such aggregates The transitional forms of foam cells and of sheets of histiocytes in these smears can be traced from clusters of apparently normal mammary epithelium PAPANICOLAOU & MADDI (1959) demonstrated the epithelial origin of the foam cells and the histiocytes by experimental transformations in tissue cultures on clusters of mammary epithelial cells They found gradual transformation of epithelial cells into free foam cells that could phagocytize erythrocytes which were purposely introduced into the cultures The ductal origin of vacuolated phagocytes in secretions from the mammary gland now seems to be generally accepted (Koss 1961)

Fibrocystic disease Of the 556 benign mastopathies listed in Table 1, 88 7 per cent were histologically classified as fibrocystic The most common yield at aspiration biopsy in these cases (in 40 4 per cent of the group) was a fluid which could be clear yellow brown, greenish or blood stained

The presence of single or multiple cysts hampers diagnostic palpation of the breast When cystic fluid is removed by aspiration the lesion can be more easily evaluated If no residual underlying mass is palpable the affected site may or may not be extirpated depending upon the routine practice at the clinic in question

Cytologic study of clear fluid aspirated from these cysts generally reveals only foamy phagocytes When a mass can be palpated after the aspiration however the fluid is usually more cell rich with inflammatory cells as well as foamy phagocytes Some smears contain epithelial cells with varying degrees of atypia and in papillary formation A palpable mass persisting after aspiration of a presumed cyst is almost always extirpated In such cases therefore the cytologist s

report will have little influence on the further management, except in the rare instances in which malignant cells from a carcinoma growing in the cystic wall are detected *in smears of the fluid aspirate*.

Benign epithelial cells without noteworthy admixture of cystic fluid were aspirated in 34.7 per cent of the cases with fibrocystic mastopathy. Smears from such lesions as a rule reveal only a few tightly packed plugs of cells. Dissociated cells are rarely seen, and if present usually display signs of degeneration (Fig. 3a). Naked nuclei with bipolar form are often encountered, however (Fig. 3b).

In most cases, there is no obvious cellular atypia, and the cytologic recognition of a benign condition presents no problem. But if, instead of this homogeneous appearance, plugs of apparently benign cells are intermingled with clusters of atypical cells, and particularly if the smears possess intact free ductal cells with nuclear atypia, the possibility of the presence of a precancerous lesion or early carcinoma must be considered (Fig. 3c). Depending upon the gravity of the cytologic indication of malignancy, the cytologist may advise frozen sectioning in connection with excision of the lesion.

In ten cases of fibrocystic mastopathy the cytologic report suggested carcinoma (Table 1), in all of which the mass and its surrounding tissue were extirpated. The cytologic and histologic slides from these cases have been reviewed. The histologic diagnosis was upheld, but in the light of present cytologic experience the slides prepared from the biopsy aspirate would be considered to indicate malignancy in only six of the cases. In one of these six cases (Fig. 6a), a carcinoma was found just beneath the operation scar two years after aspiration biopsy and excision of the initial mass, and cancerous lymph nodes were present in the axilla. The other five cases in which cytologic smears were still considered to suggest malignancy are alive and apparently free from cancer after four to seven years of observation.

The cytologic report stated carcinoma in one case (Fig. 2a) and mastectomy was performed later at another hospital. The examining pathologist reported fibrocystic mastopathy. The cytologic slides were then re-examined and, as the diagnosis of malignancy was confirmed, a study of additional tissue specimens was recommended. Unfortunately, however, the excised breast was no longer available for further analysis. This patient is apparently free from cancer five years after mastectomy.

Fibrosing adenosis. Contrary to the opinion that fibrosing adenosis is histologically 'the commonest lesion confused with breast cancer' (STEWART 1950), this lesion has not caused major problems in the present series, the reason probably being that the lesions were usually very small and fibrotic. Needling as a rule

yielded only a few atypical cells most often in acinar arrangement and intermingled with naked nuclei of benign appearance, quite unlike the findings in a carcinoma smear Malignancy was considered possible in only one case in which cell rich smears were obtained Review of the slides revealed plugs of cells partly in acinar arrangement and with marked anisonucleosis (Fig 4), which had aroused suspicion of early carcinoma

If the cytologic requirement for a diagnosis of mammary carcinoma is that the smear must be dominated by unmistakable cancer cells this should preclude false positive reports of malignancy in fibrosing adenosis

Fibroadenoma This was the most common of the benign mammary tumours in the series (Table 2) representing 89 2 per cent of the total 251 benign tumours Clinical examination characteristically reveals a firm freely mobile mass which may be confused with cyst or lipoma however and in elderly patients also with carcinoma The expected aspirates in these lesions are fluid fat and carcinoma cells respectively but in fibroadenoma benign mammary epithelium This last finding, in combination with palpation of a well circumscribed mass indicates fibroadenoma

In most cases of fibroadenoma smears prepared from biopsy aspirate contain numerous clusters of epithelial cells and also free dissociated cell elements with predominance of naked bipolar nuclei (Fig 5) This contrasts with paucity of cellular material in aspirate from cases of fibrocystic disease of the breast

Whether or not and in what frequency the cytologic features described can provide a sufficient basis for diagnosis of fibroadenoma in the absence of a clinical report of a well circumscribed tumour is not yet known This question will be tackled in future studies At present it can only be placed on record that of the 224 cases of histologically demonstrated fibroadenoma 57 6 per cent had already been thus diagnosed by the aspiration biopsy method

A false positive diagnosis of fibroadenoma was made from slides of aspirate in only 12 of the 583 cases with a subsequent histologic diagnosis of benign mammary lesions other than fibroadenoma (556 in Table 1 and 27 in Table 2) Of these twelve cases nine had fibrocystic mastopathy and three had fibrosing adenosis

Carcinoma was cytologically suspected in 12 of the cases histologically classified as *fibroadenoma* The histologic diagnosis in one of these cases was suspected cystosarcoma phyllodes When the cytologic slides of the remaining eleven cases were reviewed it was decided that with present experience only four cases would be labelled as possibly malignant and in all these four cases the tumour and surrounding tissues were excised One of the patients (with histologic diagnosis of fibroadenoma) was found 13 months later to have a subcicatricial carcinoma

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Table 5

Histologic reclassification of 33 cases with original histologic diagnosis precancerous mammary lesion

Cytologic findings	Histologic grading		
	I	II	III
Benign or no cellular material	13	9	2
Cellular atypia	—	1	—
Carcinoma suspected	—	2	2
Carcinoma	—	1	3
Total	13	13	7

This analysis of the data in Table 5 indicates that when needle biopsy smears are considered to indicate carcinoma and the case is histologically classified as intraductal carcinoma it belongs to the group of intraductal carcinomas for which histologic and clinical experiences advocate management as for invasive carcinoma

Mammary carcinoma The histologically diagnosed cases of mammary carcinoma are included in Table 3 The cytologic reports from aspiration biopsy in these cases can be grouped as negative, suggestive of carcinoma or positive for carcinoma

Malignancy was histologically proven in 867 cases and was considered probable in 6 cases A negative cytologic report as regards malignancy was given in 94 cases the yield being described as acellular material in 35 cases benign cells in 42 cases and atypical cells in 17 cases

Failure to demonstrate the presence of carcinoma in a cytologic study of needle biopsy aspirate was thus due either to failure to obtain cells from the target or to recognize the malignant nature of the aspirated cells The cytologic slides from the 94 cases of carcinoma with negative cytologic reports were therefore re examined in order to analyze the respective importance of these factors in the series Indubitable carcinoma cells were then detected in 21 cases and possibly malignant cells were seen in 10 cases (as exemplified in Fig 8) The false negative cytologic diagnoses in 31 (32 9 per cent) of the 94 cases could therefore be attributed to lack of experience in reading the slides

Review of the slides in the remaining 63 cases confirmed the absence of recognizably or suspectedly malignant cells in the smears of biopsy aspirate In two cases no mass was palpable in the breast (these cases should properly have

with axillary lymph node metastases (Fig 6b) The other three patients are apparently free from carcinoma 5 to 6 years postoperatively

'Precancerous lesion', intraductal carcinoma 'Precancerous was used in the histologic reports of 33 cases to describe lesions that were considered by the examining pathologists not to fit any generally accepted label but to be in some way related to malignancy (For a review of the literature on such lesions, the reader is referred to STEIN 1967) In these cases, the slides were collected and reviewed for a correlation of the cytologic and histologic observations The tumours were classified as groups I, II, or III according to the histologic observations

Cases with atypical intraductal proliferation of a type that prompts pathologists to recommend careful follow up, and immediate removal of all palpable lesions for histologic study, were placed in group I Thirteen cases belonged to this group Group II comprised cases with marked intraductal proliferation, and a general pattern closely resembling intraductal carcinoma but with insufficient cellular atypia to suggest the presence of undetectable invasive growth Depending upon the extent of the lesion and the general clinical picture, simple mastectomy is usually recommended in such cases, there were thirteen in our series Cases with the histologic appearances of intraductal carcinoma, and in which the cell atypia suggested undetectable invasive growth, were placed in group III With this picture, radical mastectomy is generally advised Seven cases belonged to group III

The cytologic reports in the histologically reclassified cases of precancerous lesion are collected in Table 5 None of the thirteen cases in group I were cytologically malignant Of the thirteen cases in group II, two were thought to be carcinoma and one was cytologically malignant The cytologic examination was followed in this case by simple mastectomy, the patient is well after about 4 years of observation The histologic examination and the cytologic features of this case are given in Fig 7 a and b Comparison between the cells in the smear and those in the tissue section indicates that the histologic specimen cannot be considered representative of the tumour The aspirated cells display characteristics of invasive carcinoma (cf Fig 9, c and f)

Of the seven cases in the histologic group III, two were cytologically considered malignant and three were stated to be carcinoma Of these last three cases, two underwent simple mastectomy and one radical mastectomy One of the two simple mastectomies after two years displayed appearances of metastatic axillary carcinoma, and death occurred from systemic dissemination one year later (Fig 7, c and d) The two other patients are apparently well after 4 and 5 years, respectively

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The main reason why diagnostic accuracy is higher in clinically manifest carcinoma is the abundance of malignant cells in the aspirated specimen In early carcinoma fine needle aspirate as a rule contains only a few malignant cells and correspondingly greater caution must be observed when the report is formulated The cytologist who recommends radical surgery in such a case must bear in mind that it is upon the histologic examination of the extirpated tissue that the necessity for the operation will be retrospectively judged In the present state of cytologic knowledge a definite statement of mammary carcinoma should not be based upon the presence of a few carcinoma like cells scattered among normal or atypical epithelial elements Predominance of unmistakable cancer cells should be required (Figs 9 to 12)

Among our 807 cases histologically diagnosed as benign mammary lesions there was only one definite cytologic report of malignancy (p 12) Since re-examination of the slides prepared from the biopsy aspirate in this case disclosed that the cell population consisted almost exclusively of indubitable cancer cells it is probable that the negative histologic report was due to incomplete exploration of the breast The palpable mass in this case was less than 1 cm in diameter Such small tumours are usually studied by local extirpation when frozen or paraffin embedded sections should readily reveal if carcinoma is present If the carcinoma is clinically advanced study of the whole breast likewise generally gives ready histologic confirmation of a cytologic diagnosis of malignancy But when as in the case under discussion a scarcely palpable lesion is revealed by aspiration biopsy to be carcinoma and the whole breast is fixed in formalin and sent for histologic examination even close collaboration between cytologist surgeon and pathologist may not avail to secure proof of malignancy In some such cases we have succeeded in establishing the diagnosis only after study of serial sections from 10 to 20 specimens of mammary tissue Because this difficulty is recognized we sometimes recommend a frozen section after local extirpation and before radical surgery even if we are convinced from the cytologic examination that a carcinoma is present viz in clinically doubtful cases when the histologic examination will not be made at the Institute of Radiopathology

It is thus clear that when fine needle biopsy is adopted for routine use in the diagnosis of mammary carcinoma heavy demands are made on the cytologist's formulation of his report and on the clinician in evaluating it The danger of false positive and false negative cytologic diagnoses in this condition has frequently been demonstrated in the literature Some pertinent data are presented in Table 6 Only series with 80 or more verified carcinoma cases are included in this table

The total of cases surveyed in Table 6 is 3 245 all of which were studied both histologically and cytologically The histologic studies revealed carcinoma in

been excluded from this series of palpable mammary lesions), the puncture was made blind', since previous aspiration biopsies of enlarged axillary lymph nodes had indicated carcinoma, most probably metastatic from a primary mammary tumour

Of the 61 cases with a palpable mass and false negative cytologic reports, 47 per cent displayed some clinical signs of mammary carcinoma, such as dimpling of the skin, retraction of the nipple or fixation to muscle The corresponding figure in the 117 cases in which sufficient cellular material was obtained to permit a cytologic indication of mammary carcinoma (Table 3) was only 44 per cent In our opinion, therefore, the main reason for the false negative reports in these cases was not failure to reach the target, but the inability to collect malignant cells from tumours that were possibly fibrotic or had a relatively low cell content This assumption is supported by the fact that repeat needle biopsy in nine of the false negative cases yielded carcinoma cells in only three cases A more detailed analysis of this problem will be attempted in later investigations, when the cellularity of smears prepared from biopsy aspirate in mammary carcinoma will be compared with the histologic features in the same cases

'Suspected carcinoma was stated in the cytologic report in 117 of the histologically positive cases (Table 3) This cytologic diagnosis implies that the examining cytologist was fairly sure that carcinoma cells were present but was unwilling to accept responsibility for a radical operation before his opinion had been confirmed by excisional biopsy and frozen sectioning (Fig 3c) The justification of this attitude is apparent from Tables 1 and 2, 23 cases (11 in Table 1 and 12 in Table 2) were thus cytologically considered possibly malignant but subsequent histologic analysis revealed benign lesions in 22 cases and probable cystosarcoma phyllodes in one case As already stated, present experience would, in addition to the last case, uphold the cytologic probability of malignancy in only ten of these twenty three cases However, since in two of the ten cases a carcinoma formed beneath the scar after local excision of the lesion, careful follow up would seem advisable when an experienced cytologist has suspected malignancy, even though a negative histologic report has been given

Carcinoma was cytologically diagnosed in 662 (75 8 per cent) of the histologically confirmed cases in Table 3, in these cases the cytologist recommended radical operation Some of the mentioned clinical signs of carcinoma were present in 64 per cent of the 662 cases at the time of aspiration biopsy If it is recalled that the frequency of such clinical signs was 44 per cent in the cases cytologically thought to be malignant and 47 per cent in the cytologically false negative cases, it is evident that the stage of the disease had some bearing on the formulation of the cytologic report

Finally, in comparing published series of cases one must also take into account that skill in performing the needle biopsies and in reading the slides may not have been equal when the respective series were begun This too may help to explain variations in the results

The improvement that can be expected as experience accumulates can be seen by comparing our total series (from 1955 to 1963) with the results obtained in the year 1962 (ZAJICEK 1965), i e after many years of routine performance of aspiration biopsy and long practice in reading of the slides In that year 417 women underwent aspiration biopsy of the breast and subsequent mammary surgery In 190 of these the histologic examination revealed carcinoma (59 4 per cent of the 190 were clinically considered to be carcinoma prior to the aspiration biopsy examination) The cytologic report stated carcinoma in 151 of the 190 histologically proven carcinoma cases and suspected malignancy in 24 others of the same group Thus in 15 cases (7 9 per cent) a cytologically negative report was given This percentage of false negatives compares well with the 7 4 per cent in the ZAJDELA (1953) study and is the lowest figure that we have as yet obtained Such a degree of accuracy is probably obtainable only when the cytologist who reads the slides also performs the aspiration biopsy and has had long experience in these fields Repeat biopsies after negative reports in clinically doubtful cases may to some extent further improve the results But since even repeated negative needle biopsies do not ensure that a lesion is benign surgical biopsy should be performed in all clinically doubtful but cytologically negative cases

No false positive cytologic diagnosis of mammary carcinoma was made during 1962 We believe that the possibility of false positive diagnoses for this tumour may be disregarded if the cytologist is fully conversant with the morphology of the cells of the mammary gland in various pathologic conditions and if he respects the mentioned reservations concerning cases of early carcinoma

The possibility of risk to the patient is another important question In the present series of more than 3 000 cases there were no significant complications of needle biopsy of the breast Haematomas occasionally formed particularly in carcinomatous breasts but these haematomas did not cause appreciable discomfort Much more important is the possible danger of malignant dissemination No matter how fine are the needles used for aspiration biopsy the procedure will inevitably produce microtrauma in its passage through the tissues (Fig 13) with consequent risk of tumour spread locally via the needle track or distally through punctured blood or lymph vessels In our series however we found no clinical signs of local seeding of carcinoma following aspiration biopsy nor is this seeding to be expected since when a carcinoma is proven it is either widely excised or is irradiated

Table 6

Frequencies of false positive and false negative reports from aspiration biopsy in cases of histologically verified mammary gland lesion

Literature	No. of breasts	Histologically proven carcinoma		Aspiration biopsy			
				False positives		False negatives	
		No.	%	No.	%	No.	%
CORNILLOT & VERHAEGHE (1959)	500	258	(51.6)	4	(1.7)	41	(15.9)
SMITH et coll. (1959)	202	80	(39.6)	3	(2.5)	19	(23.8)
SHILLER, VOLKOVA & AGAMOVA (1960)	263	165	(62.7)	4	(4.1)	44	(26.7)
ZAJDELA (1963)	600	417	(69.5)	1	(0.5)	31	(7.4)
Present series	1 680*	873	(52.0)	1	(0.1)	94	(10.8)
Total	3 245	1 793	(55.3)	13	(0.9)	229	(12.8)

* 33 cases histologically considered as precancerous lesion not included.

1 793 cases. Among the remaining histologically benign cases there were 13 (0.9 per cent) cytologically stated to be carcinoma; of these thirteen false positive cases no less than seven were histologically proved to be fibroadenoma.

Failure of the aspiration biopsy cytologic method to disclose malignancy occurred in 229 of the carcinoma cases in Table 6. The frequency of false negative reports varied however widely: from 7.4 per cent (ZAJDELA 1963) to 26.7 per cent (SHILLER, VOLKOVA & AGAMOVA 1960). These differences become more understandable if the probable variations in the composition of the separate series are considered. Thus, the percentages of histologically proven carcinoma cases ranged from 39.6 (SMITH et coll. 1959) to 69.5 (ZAJDELA 1963). The selection of cases for aspiration biopsy and subsequent surgery may influence the accuracy of the cytologic diagnosis.

Another potential influence on the cytologic report is the number of aspiration biopsies made in the particular case. In the present series and in that reported by SMITH et coll. (1959), only the first biopsy readings are tabulated. Repetition of biopsies after initial negative reports may be expected to reduce the number of false negative diagnoses; the reduction was from 23.8 to 7 per cent in the series presented by SMITH et coll. (1959).

Whether the cytologist himself performs the aspiration biopsy, as in the present series and in that of ZAJDELA (1963) and of CORNILLOT & VERHAEGHE (1959), or reads slides sent in from outside sources is yet another factor of possible importance.

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* 33 cases histologically considered as precancerous lesion not included

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Failure of the aspiration biopsy cytologic method to disclose malignancy occurred in 229 of the carcinoma cases in Table 6 The frequency of false negative reports varied however widely from 7 4 per cent (Zajdela 1963) to 26 7 per cent (Shiller Volkova & Agamova 1960) These differences become more understandable if the probable variations in the composition of the separate series are considered Thus the percentages of histologically proven carcinoma cases ranged from 39 6 (Smith et coll 1959) to 69 5 (Zajdela 1963) The selection of cases for aspiration biopsy and subsequent surgery may influence the accuracy of the cytologic diagnosis

Another potential influence on the cytologic report is the number of aspiration biopsies made in the particular case In the present series and in that reported by Smith et coll (1959) only the first biopsy readings are tabulated Repetition of biopsies after initial negative reports may be expected to reduce the number of false negative diagnoses, the reduction was from 23 8 to 7 per cent in the series presented by Smith et coll (1959)

Whether the cytologist himself performs the aspiration biopsy as in the present series and in that of Zajdela (1963) and of Cornillot & Verhaeghe (1959), or reads slides sent in from outside sources is yet another factor of possible importance

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Distal dissemination via blood or lymph vessels, with its unfavourable implications for prognosis, is a more problematic aspect. It has been carefully investigated by a research group at the Memorial Center in New York (Robbins et coll. 1954, Berg & Robbins 1962). They registered the survival times in 1406 cases of mammary carcinoma that were submitted to radical surgery and compared the survival rates of those with and, respectively, without aspiration biopsy. *The two groups did not differ* as regards ten year survival rates. The writers therefore concluded that aspiration biopsy is not detrimental to the patient and *that 'clinically, no reason can be found* not to use aspiration biopsy when it is indicated'.

Acknowledgement

The authors take this opportunity of thanking Prof. Lars Santesson of the Institute of Radiopathology for his review of the histologic characteristics of the tumours.

SUMMARY

The value of aspiration biopsy in carcinoma of the breast was studied in 3 119 breasts in 2 937 women over a nine year period. In 1 406 of these breasts no histologic confirmation of the diagnosis was made but in 1 713 breasts the cytologic findings could be compared with the histologic reports after surgery. The accuracy of cytologic examinations of biopsy aspirate is evaluated from the present series and from reports in the literature.

ZUSAMMENFASSUNG

Der Wert der Punktionscytologie bei der Diagnose des Brustkrebses wurde über eine Reihe von Jahren an *2 937 Frauen* mit Veränderungen *in 3 119 Brustdrüsen studiert.* In 1 406 von *diesen Fällen* wurde keine histologische *Diagnose gestellt. Eine solche* war bei 1 713 Brustveränderungen vorhanden, sodass man hier die zytologischen Befunde mit den histologischen vergleichen konnte. Die Zuverlässigkeit der Punktionsmethode wurde auf Basis der eigenen Resultate und derjenigen in der Literatur kritisch geprüft.

RÉSUMÉ

Les auteurs ont étudié l'intérêt de la biopsie par aspiration dans le cancer du sein sur 3 119 seins chez 2 937 femmes sur une période de 9 ans. Dans 1 406 de ces seins *il n'y a* pas eu de confirmation histologique du diagnostic, mais dans 1 713 seins le résultat de *l'examen cytologique* a pu être comparé avec le résultat histologique après opération. Les auteurs jugent l'exactitude de l'examen cytologique dans la biopsie par aspiration d'après la présente série et d'après la littérature.

FROM THE DEPARTMENT OF RADIOLOGY (DIRECTOR PROF TADASHI MIYAKAWA) FACULTY OF MEDICINE UNIVERSITY OF TOKYO, AND THE BROADCASTING SCIENCE RESEARCH LABORATORIES JAPAN BROADCASTING CORPORATION (NHK) TOKYO JAPAN

MODULATION TRANSFER FUNCTION OF THE INTENSITY DISTRIBUTION OF THE ROENTGEN FOCAL SPOT

by

EIICHI TAKENAKA KOJIRO KINOSHITA and ROKUHIKO NAKAJIMA

In roentgen image transmission systems many factors are basically related to image quality Some of the intensity distributions of the *roentgen focal* spot and its modulation transfer function (MTF) have been experimentally measured However no definite standardization of the intensity distribution of the focal spot and no generalized study of relationships to the modulation transfer function seem to have been made (see NBS Handbook No 89 (1963))

The intensity distribution of the focal spot is in this report expanded to symmetry and anti symmetry components on a base of rectangular function The parameters of the *symmetry* and anti symmetry components are presumed and the relations to the modulation transfer function are clarified Thus the effective intensity distributions of the focal spot are standardized by the use of its modulation transfer function These results are indispensable for the analysis and standardization of roentgen systems such as roentgen television and cineradiographic equipment and are of basic importance for the study and interpretation of roentgen images

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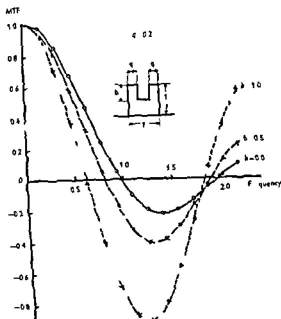


Fig 2 Modulation transfer function of twin peaked symmetric intensity distribution of the focus

where $f(x)$ is a base of function $g_s(x)$ are symmetry components, $g_{as}(x)$ are anti symmetry components and k_0, k_s and k_{as} are coefficients

Then the Fourier transform is

$$G(f) = k_0 F_0(f) + k_s G_s(f) + k_{as} G_{as}(f) \tag{1}$$

where $G(f)$ $F_0(f)$ $G_s(f)$ and $G_{as}(f)$ are Fourier transforms of $g(x), f(x)$ $g_s(x)$ and $g_{as}(x)$ respectively and f is a spatial frequency (lines *per unit length*). The approximation of the rectangular distribution is more convenient to determine than that of the Gaussian. In order to do so the height and width of the focal roentgen intensity distribution are supposed to be of unit length 1. Parameters b c and q in Figs 2 to 7 indicate b depth of the valley, c half of the difference between the two peaks (or grade of anti symmetry) and q the width of the peak

Intensity distribution and its modulation transfer function (MTF)

1 MTF of twin peaked intensity distribution

Let $g(x)$ be the intensity distribution (Fig 2). Its distribution is decomposed into three components that is rectangular distribution of $(1-b)$, symmetric rectangular of qb and anti symmetric rectangular of qc. They are to be linearly

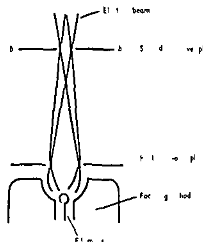


Fig. 1. Schematic track of electrons converged by an electrostatic focusing lens in a conventional roentgen tube.

Decomposition of intensity distribution of focal spot into symmetry and anti-symmetry components

The roentgen intensity distribution of the focal spot is dependent on the material, coarseness and inclination of the anode, the vibration of the rotating system, the energy of the electrons and the shape of the electron beam (affected by filament voltage, tube voltage and tube current).

In conventional medical roentgen tubes, the electrostatic focusing system focuses thermal electrons from its cathode on a spot of the anode. The thermal electrons from the upper right or left half of the filament are focused on one spot of the anode, and those from the lower right or left half of the filament are focused on the other spot. They cross over each other first in the plane of *a—a* and a second time in the plane of *b—b* as a result of the focusing electrostatic field. The former is called the main focal spot and the latter the accessory focal spot (Fig. 1). The second cross-over plane of *b—b* is used in conventional medical roentgen tubes, in which the intensity distribution is twin peaked. Triple or quarternary intensity distributions depend on whether the focal plane is displaced forward or backward from the plane of *b—b*.

In conventional roentgen tubes the single-peaked intensity distribution cannot be generally used at the point of roentgen output, either momentarily or continuously. However, it may be obtained in the special roentgen tube of Pierce gun structure which is used in enlargement radiography. All the intensity distributions of the focal spot can be approximately decomposed into rectangular symmetry and anti-symmetry components with the center of the roentgen beam. The one-dimensional focal roentgen intensity distribution of $g(x)$ is shown as follows:

$$g(x) = k_0 f_0(x) + k_s g_s(x) + k_{as} g_{as}(x)$$

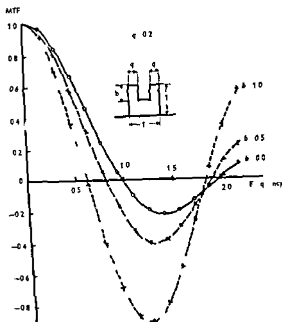


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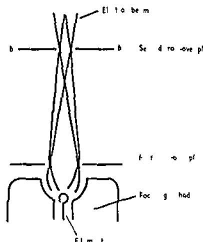


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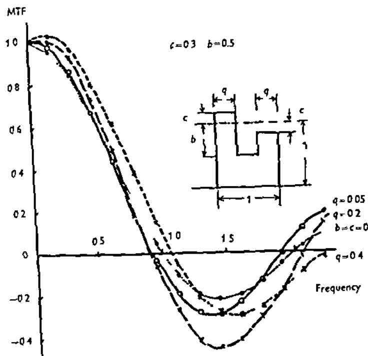


Fig 4 Modulation transfer function of twin peaked anti symmetric intensity distribution of focus

used in television and optical systems Because roentgen imaging systems contain television and optical systems the overall images and every component in roentgen imaging system should be systematically evaluated from the same standpoint as in the television and optical systems In television systems the cut-off frequency (f_c) is assumed as the one at the 70 7 % decrement of the MTF that is −3 dB (NHK Handbook Japan Broadcasting Corporation Tokyo 1964) in order to compensate for the characteristics of images If the f_c at the lower amplitude of the MTF that is the broad pass band of the rectangular function is taken the compensation of characteristics will increase the noise and will deteriorate the image quality In this paper therefore the identical f_c in focal intensity distribution is used as in the television system The relative cut-off frequency (f_{rc}) is defined as the ratio of the above cut off frequency of the focus with peaks to that without peaks The f curves of the symmetric twin peaked intensity distribution are obtained

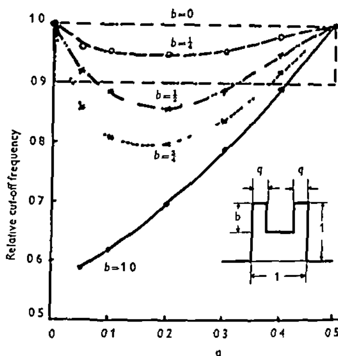


Fig 3 Distribution parameters of twin peaked symmetric focus and associated cut off frequency

combined with one another, so the above equation is deductively calculated as follows (appendices)

$$G_{tw}(f) = (1-b)\frac{\sin \pi f}{\pi f} + 2qb \cos\left\{2\pi f(1-q)/2\right\}\frac{\sin \pi q f}{\pi q f}$$

$$- 2qc \sin\left\{2\pi f(1-q)/2\right\}\frac{\sin \pi q f}{\pi q f}$$

$$= (1-b)\left[F_0(f) + \frac{2qF(f)}{1-b}\left\{b \cos \underline{(1-q)a} - c \sin \underline{(1-q)a}\right\}\right] \qquad (2)$$

where $F_o(f) = (\sin a)/a$, $F(f) = (\sin qa)/qa$, $a = \pi f$

This parameter c has negative values when the left peak of asymmetric distribution is higher than the right peak and has positive values when the left peak is lower

1—A Symmetric twin peaked intensity distribution If we let $c = 0$ in eq (2), we obtain

$$G_{tw}(f) = (1-b)F_0(f) + 2qF(f)b \cos \underline{(1-q)a} \qquad (2\,)$$

The deeper the valley b of the symmetric twin peaked one in Fig 2, the more the decrease of MTF in the low frequencies The MTF is routinely

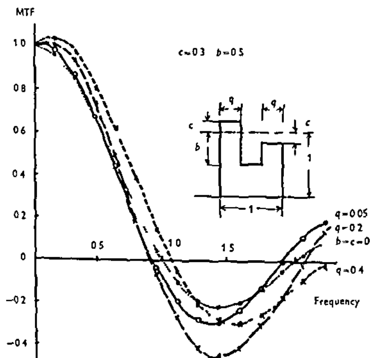


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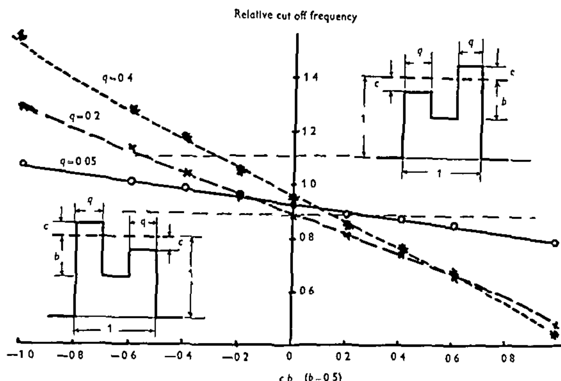


Fig 5 Distribution parameters of twin peaked anti symmetric focus and associated cut off frequency

from their MTF with $b = 0$, 1/4, 1/2, 3/4 and 1 0 If a 10 % decrement of the f_{rc} is to be permitted, the depth b of the valley of the focal spot cannot be more than 0 4 If $b = 0.5$, the parameter of q should be less than 0 08, or more than 0 33 Even if $b > 0.4$, the f_{rc} can be within — 10 % variation in $q = 0$ and $q = 0.5$ But, the steep gradients of the f_{rc} (c/b) curves at $q = 0$ and $q = 0.5$ produce a large variation of f_{rc} from a slight change in q For this reason, the parameter b must be less than 0 4 If the parameters b and q from the measured focal intensity distribution are not over the dotted lined enclosure (Fig 3), the decrement of the f_{rc} in the focal spot must be within — 10 %

1—B Asymmetric twin peaked intensity distribution It is not always bad in MTF for the deeper depth of valley, not as likely as in the symmetric one This MTF is asymmetric and is more than 1 0 in the vicinity of $f = 0$ The larger the parameter of c in the higher right peak, the smaller is the f_{rc} If a 10 % decrement of the f_{rc} is to be permitted, there cannot be $q = 0.2$, for the f_{rc} is less than 0 9 ($f > 0$) If $q = 0.05$, $c/b = 0.25$, or $q = 0.4$, c/b =

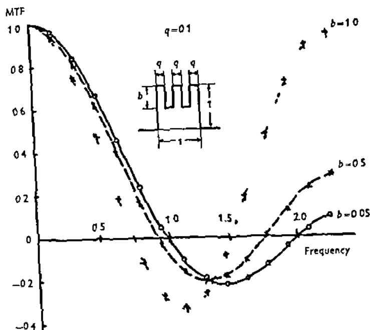


Fig 6 Modulation transfer function of triple peaked symmetric intensity distribution of focus

0 12 the decrement of the f_{re} can be within 10 % In order to depress the variation of the f_{re} within $\pm$ 10 % the parameters of c/b and q should be within the domain of $f_{re} = 0\,9 \sim 1\,1$ (Figs 4 and 5)

2 *Triple peaked intensity distribution*

This distribution has an additional peak in the center of the twin peaked distribution This is decomposed into four components rectangular ones of $(1-b)$ and qb symmetric rectangular of qb and anti symmetric of qc Then its Fourier transform $G_{tr}(f)$ is given as follows

$$G_t(f)=(1-b)\left[F_0(f)+\frac{q}{1-b}F(f)\left\{2b\cos\underline{(1-q)a}-2c\sin\underline{(1-q)a}-b\right\}\right] \quad (3)$$

where $F_0(f) = (\sin a)/a$ $F(f) = (\sin qa)/qa$ The parameter c shows the antisymmetry components and has negative values in the higher left peak of the spot as in the asymmetric twin peaked distribution

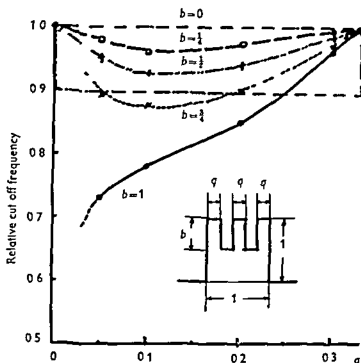


Fig 7 Distribution parameters of triple peaked symmetric focus and associated cut off frequency

2—A Symmetric triple peaked intensity distribution has a much better MTF than the twin peaked one The amplitude at a level higher than the second zero frequency reaches 1 0 (Fig 6) But such high spatial frequencies of the object are not relevant because they cannot be transmitted by a roentgen imaging system with film and fluorescent screens without being obscured by scattering The decrement of f_{rc} is smaller than that of the twin peaked one In order to enclose the variation of the f_{rc} within — 10%, the depth of valley b should be less than about 0 6 if possible Even if $b > 0\ 6$, the f_{rc} may be within — 10 % variation in the vicinity of $q = 0$ and $q = 0\ 5$ Its reason is similar to the symmetric twin peaked focus The f_{rc} of the triple peaked type does not become worse than the twin peaked, even if the valley of the former is deeper than that of the latter (Fig 7)

2—B Asymmetric triple peaked intensity distribution has nearly the same MTF as in the rectangular distribution without peak and valley The amplitude at levels higher than the first zero frequency (spurious resolution) is smaller than the twin peaked one The asymmetry of this type and the decrement of the f_{rc} are smaller than those of the twin peaked one The selection of q and c/b is standardized as in the asymmetric twin peaked distribution

The MTF in Fig 2 shows that the single peaked focus of 1 mm × 1 mm, for example has a spurious resolution at a frequency higher than 1 line/mm and that the isolated two-peaked focus has the spurious resolution at a frequency higher than 0 6 lines/mm The MTF of the asymmetric focus can be more than 1 0 in the vicinity of the origin It is asymmetric as a whole and has a shifted origin As is well known in photography, the adjacency effect brings forth such a shift in MTF Caution however, should be employed in relation to the asymmetric distribution of a focal spot which shows such a MTF Even if the decrement of the f_{re} is within permissible limit in the positive frequency domain some may be out of the limits in negative frequencies This makes the asymmetric distribution of the focal spot inferior to the symmetric distribution The single peaked intensity distribution of the focal spot is ideal as regards its MTF and f_{re} In conventional medical roentgen tubes however it is generally twin peaked or triple peaked due to (1) the momentary and continuous heavy load and (2) the high cost of roentgen equipments In order to make the most effective use of the radiation from the focal spot its dimensions or the parameters of its intensity distribution should be determined as outlined in this paper But the decrement percentage of the f_r is determined by the frequency characteristics of the object necessary to diagnose or those of the focus with the permissible load of roentgen tubes

Appendices

1 *Definition of a base and Fourier transform* As the intensity distribution of the focal spot is approximated by means of rectangular distribution let $f(x)$ be the following rectangular intensity distribution of the focal spot

$$f(x) = \begin{cases} A & -x_0/2 < x < x_0/2 \\ O & \text{otherwise} \end{cases}$$

then its Fourier transform $F_0(f)$ is

$$F_0(f)=\int_{-\infty}^{\infty} f(x)\exp(-2f\pi xi)\,dx = Ax_0\,(\sin \pi x_0 f)/\pi x_0 f$$

where f is a spatial frequency (lines / unit length)

2 *Linearity* Let the intensity distribution be $af(x)$ its Fourier transform is $aF(f)$ And let the intensity distribution be $f_1(x) \pm f_2(x)$ its Fourier transform is $F_1(f) \pm F_2(f)$

3 *Shifting theorem of Fourier transform* Let $f(x)$ shift x_0 on the x axis and

$$f(x-x_0) = \begin{cases} B & x_0 - D/2 < x < x_0 + D/2 \\ O & \text{otherwise} \end{cases}$$

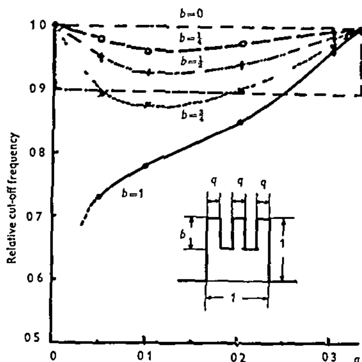


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2—B *Asymmetric triple peaked intensity distribution* has nearly the same MTF as in the rectangular distribution without peak and valley. The amplitude at levels higher than the first zero frequency (*spurious resolution*) *is smaller* than the twin peaked one. The asymmetry of this type and the decrement of the f_{rc} are smaller than those of the twin peaked one. The selection of q and c/b is standardized as in the asymmetric twin peaked distribution.

FROM THE DEPARTMENT OF RADIATION THERAPY, UNIVERSITY HOSPITAL, TURKU
FINLAND

SIGNIFICANCE OF FOCUS SIZE IN IRRADIATION THERAPY

by

P. KLAMI

It is customary in roentgen tube manufacture to reduce the size of the penumbra by means of a small focus. This applies particularly to tubes used in roentgen diagnosis, whereas the requirements in this respect are less stringent in roentgen therapy; a small focus is however always considered an advantage as long as it does not excessively restrict the loading of the anode.

Radiation sources of large area dimensions have also been employed; these have mainly been made of radioactive material. Examples are certain tele-radium units (BENNER 1937), radium containing plate applicators and moulages and solutions of radioisotopes. Roentgen sources of large area have been designed for specific purposes: for deep therapy by WITTE, ZIMMER & KESSLER (1939), BARTOW et coll. (1949) and by COLOMBO & LENZI (1951); for roentgen television by MOON (1948) and KLAMI (1963); for technical applications by HOFMANN & DIETRICH (1965) and for superficial radiotherapy by KLAMI (1965). The reason why these sources have not been developed is mainly that their practical significance has not been fully realized; thus there has been no economic incentive to those who would have the resources to investigate and manufacture them.

Submitted for publication 6 April 1967.

then its Fourier transform is

$$G(f) = \int_{-\infty}^{\infty} f(x-x_0)\exp\{-2f\pi(x-x_0)i\}dx = \exp(-2f\pi i x_0)\, F(f)$$

where $F(f) = BD(\sin \pi Df)/\pi Df$

	Function	Fourier transform
4 *Symmetry*		
	$g(x) = f(x+x_0) + f(x-x_0)$	$G(f) = 2\cos 2\pi f x_0 F(f)$
where	$f(x+x_0) = f(x-x_0)$	
5 *Anti symmetry*		
	$g(x) = f(x+x_0) + f(x-x_0)$	$G(f) = -2\sin 2\pi f x_0 F(f)$
where	$f(x-x_0) = -f(x-x_0)$	

SUMMARY

The intensity distribution of the roentgen focal spot is expanded to symmetry and anti symmetry components on a base of rectangular function The parameters of its distribution are standardized by its modulation transfer function and relative cut off frequency The parameters should be determined by the decrement of relative cut off frequency The asymmetric focus has an asymmetric modulation tran fer function with a shifted origin

ZUSAMMENFASSUNG

Die Intensitatsverteilung des Rontgenbrennfleckes wird in Symmetrie und Anti Symmetrie Komponente auf rechtwinkliger Funktionsbasis entwickelt Die Parameter der Intensitatsverteilung werden auf Basis ihrer Modulationsubertragungsfunktion und relativer cut off Frequenz standardisiert und sollen aus der relativen cut off Frequenz bestimmt werden Die Modulationsverteilungsfunktion des unsymmetrischen Fokus ist unsymmetrisch mit Verschiebung des Origins

RÉSUMÉ

La distribution spatiale de l intensite du foyer focale est transformée en composants symétriques et anti symétriques ayant pour base une fonction rectangulaire Les paramètres de cette distribution sont exprimés par leur fonction de transfert de modulation et la fréquence limite de cut off Les paramètres peuvent être déterminés par la décroissance de la fréquence limite relative Le foyer asymétrique a une fonction de transfert de modulation asymétrique avec déplacement de l origine

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proportionally to the distance so that the area has increased in proportion to the square of the distance

If the side of an irradiated square on the surface of an object O is denoted by a_O and that of a square area within the object by a_T and the corresponding radiation intensities by I_O and I_T we have

$$\frac{I_T}{I_O}=\frac{a_O^2}{a_T^2}=\frac{PO^2}{PT^2} \qquad (1)$$

from which follows that

$$I_T=I_O\frac{PO^2}{PT^2}$$

If under otherwise similar conditions the area of the radiation surface F is large (Fig 1 upper right) it may be theoretically replaced by a point like focus P located farther from the object If we denote by f the length of the side of the focus F we may write

$$\frac{PO}{PO-FO}=\frac{a}{f} \text{ or } PO=\frac{a}{a-f}\,FO$$

Hence

$$I_T=I_O\left(\frac{\frac{a}{a-f}\,FO}{\frac{a}{a-f}FO+OT}\right)^2$$

or

$$I_T=I_O\left(\frac{a\ FO}{a\ FO+(a-f)\ OT}\right) \qquad (2)$$

The change in radiation intensity with increasing distance has decreased as a result of the increase in the size of the focus When f equals a I_T is equal to I_O This may also be stated as follows

If the area of the focus is increased until it becomes equal to the area of the object (surface O in Fig 1 middle left) this implies a shift of the assumed point P to infinity ($PF=\infty$) and hence the ratio of the distances PO and PT is unity

Hence

$$\frac{PO^2}{PT}=1 \text{ and } I_T=I_O$$

The difference in distance would then be of no significance This is however only speculative It could be the case in practice if we could delimit the cone of radiation emerging from every point P of the focus F *so much that its peak*

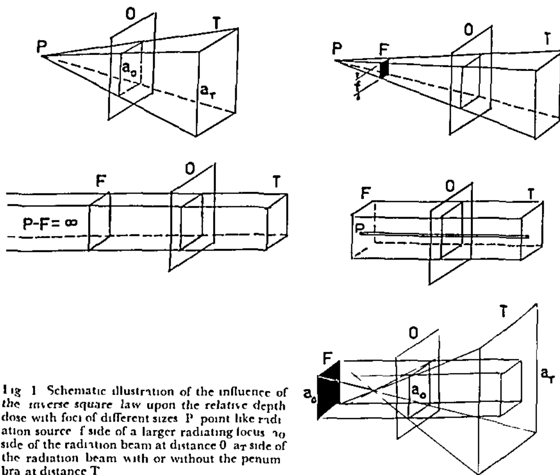


Fig 1 Schematic illustration of the influence of the inverse square law upon the relative depth dose with foci of different sizes P point like radiation source f side of a larger radiating focus a_0 side of the radiation beam at distance 0 a_T side of the radiation beam with or without the penumbra at distance T

The significance of the size of a plane anode in radiotherapy will be considered in this communication The influence of size when concave and convex anode surfaces are used will be discussed in another publication

The ratio of the radiation doses within and on the surface of an irradiated object, the so called per cent depth dose, is determined not only by the absorbed and scattered radiation within the material of which the object is composed, but also to a large extent by the focus object distance When the radiation intensity is measured or calculated, no true point sized radiating focus exists in practice, nor even a point sized measuring instrument A theoretical 'point concept is however used in the following to illustrate the dependence of radiation intensity on the focus object distance, on the size of the focus and on other associated factors Absorption and secondary radiation are disregarded

The inverse square law is well known (see Fig 1, upper left) the radiation emerging from a point like focus *P* diminishes with the distance from *PO* to *PT* because it spreads over a square surface the side of which has increased

tion from only some of the points of the focus impinges on an area the penumbra outside this field The intensity of the radiation in the penumbra diminishes as the distance from the centre increases and the source points from which radiation enters the penumbra decrease in number If we denote by a_T the length of the side of the penumbra area we get

$$\frac{a_T}{a_O}=\frac{\frac{FO}{2}-OT}{\frac{FO}{2}}$$

and

$$a_T^2=\left(a_O+2\frac{OT}{FO}\ a_O\right)^2 \qquad (3)$$

The total area exposed to the radiation thus increases with depth and with decreasing distance from the focus to the irradiated field Especially in contact therapy (*FO* small) the size of the penumbra and the resulting excessive volume dose already preclude the use of a large focus area without separate collimation of the conical radiation beams

If as in Fig 2 a and b the conical beam emerging from each point of the anode is collimated so it becomes relatively limited and a truncated cone *C* with a peak angle equal to the peak angles of the separate conical beams is used to limit the anode area and irradiated field the following advantages are obtained

1 The irradiation of the object surface becomes more uniform than in the conditions outlined above This is particularly so the greater the number of conical beams that fall on a point on the object surface i e the greater the number of foci per unit area of the anode the larger the peak angles of the conical beams and the larger the focus-object distance The last condition is not stringent if the first two conditions are fulfilled Fig 2 c indicates that the anode surface area must be larger than the irradiated area of the object If we denote by D_F the diameter of the former by D_O the diameter of the latter by α half the peak angle of the conical beam and by R the radius of the anode surface area irradiating a single point on the object surface then

$$\frac{R}{FO}=\text{tang}\ \alpha \quad R=FO\ \text{tang}\ \alpha$$

and

$$D_F=2\ FO\ \text{tang}\ \alpha+D_O \qquad (4)$$

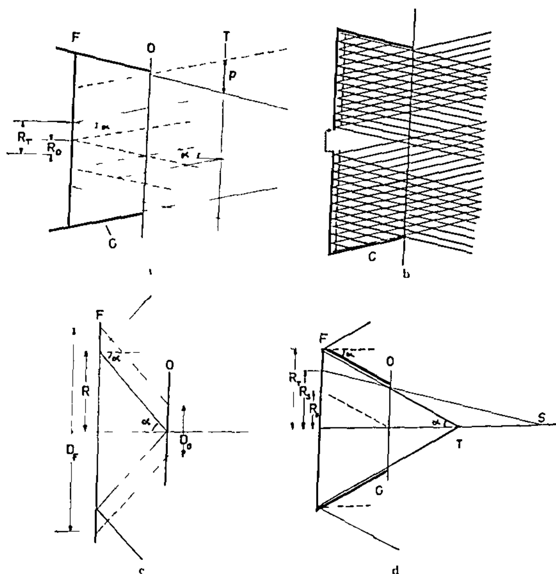


Fig 2 Collimated radiation beams from a roentgen source of large area

angle would be zero (Fig 1, middle right), i e if we could arrange so that the radiation emerging from the whole focal surface F were parallel, its divergence according to the inverse square law would not occur

If, as the other extreme (Fig 1, lower right) the radiation cone is not limited at all (peak angle 180°), a field equal in area to the focus will be formed at distance T and this field will be non homogenous, with a slightly greater intensity of radiation at the centre than elsewhere in the field This irradiated field is composed of the points struck by radiation from all points of the focus Radia

tion from only some of the points of the focus impinges on an area the penumbra outside this field The intensity of the radiation in the penumbra diminishes as the distance from the centre increases and the source points from which radiation enters the penumbra decrease in number If we denote by a_T the length of the side of the penumbra area we get

$$\frac{a_T}{a_O}=\frac{\frac{FO}{2}+OT}{\frac{FO}{2}}$$

and

$$a_T{}^2=\left(a_O+2\frac{OT}{FO}\ a_O\right)^2 \qquad (3)$$

The total area exposed to the radiation thus increases with depth and with decreasing distance from the focus to the irradiated field Especially in contact therapy (*FO* small) the size of the penumbra and the resulting excessive volume dose already preclude the use of a large focus area without separate collimation of the conical radiation beams

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$$\frac{R}{FO}=\text{tang}\ a \quad R=FO\ \text{tang}\ a$$

and

$$D_F=2\ FO\ \text{tang}\ a+D_O \qquad (4)$$

In practice this limits the magnitude of the peak angle

2 The penumbra can be reduced to moderate size It is demonstrated in Fig 2a that when the 'peak angle' of the penumbra is $2a$ and p is its width at depth OT, then

$$p = 2\ OT\ \text{tang}\ a \tag{5}$$

Also, the reduction of the penumbra requires a suppression of the peak angle

3 From the collimation of the conical beams it follows (Fig 2a) that radiation falls on a point on the surface of the object O from a smaller area of the anode surface I (from an area of diameter R_O) than on a point at a greater distance T from the object surface (from an area of diameter R_T) The ratio of the circular areas

$$\frac{\pi R_T^2}{\pi R_O^2}$$

may be called the geometric factor GF, the intensity of the radiation increases with distance in proportion to this ratio

$$\frac{R_O}{IO} = \text{tang}\ a \quad \text{and} \quad \frac{R_T}{IT} = \text{tang}\ a$$

and hence

$$\frac{R_O}{IO} = \frac{R_T}{IT} \quad \text{and} \quad \frac{R_T}{R_O} = \frac{IT}{IO}$$

regardless of the magnitude of the angle a, and

$$GF = \frac{\pi R_T^2}{\pi R_O^2} = \left(\frac{IT}{IO}\right)^2$$

Superposition of the conical beams thus leads to a geometric increase in the radiation intensity which is proportional to the square of the ratio of IT to IO On the other hand, eq (1), divergence of the conical beams produces a converse change in the radiation intensity according to the inverse square law This decrease in intensity is also proportional to the square of the ratio of these same distances

These two changes in intensity thus cancel each other, the distances lose their significance, and the intensity diminishes as in parallel radiation only owing to absorption and secondary scattering radiation

This conclusion is valid up to a certain distance, which depends on the magnitude of the anode area and the peak angle a (Fig 2d) The following equation gives the relationship between the desired geometric maximum

depth OT the focus object distance FO the radius R of the anode and the peak angle of the collimated conical beams

$$\frac{R_T}{FO+OT}=\text{tang }a \qquad (7)$$

As indicated in Fig 2d the geometric factor decreases in value again with increasing depth S ($> T$) because the radius of the anode area that irradiates point S decreases to the value R_S whereas the radius of the anode area that irradiates a point of the object surface remains constant (R_O) Thus

$$\frac{R_S}{R_T-R_O}=\frac{FS}{OS} \text{ and } GF_S=\left(\frac{R_S}{R_O}\right)^2=\left[\frac{(R_T-R_O)\ FS}{OS\ R_O}\right]^2$$

When $R_O=FO$ tang a is substituted

$$GF_S=\frac{(R_T-FO\ \text{tang }a)(FO+OS)}{OS\ FO\ \text{tang }a} \qquad (8)$$

4 The difficulties associated with the juxtaposition of the two treatment fields are well known either an untreated zone between the fields remains or an excessive dose falls on a zone where the fields are superimposed (HENSCHKE 1943 and others) These disadvantages can be largely eliminated by using the arrangement of several overlapping irradiated fields as shown in Fig 2b

Discussion

As the focus object distance does not influence the relative depth dose when numerous collimated radiation beams are employed it would of course be advantageous to increase the intensity by decreasing the distance As noted in par 1 p 277 however the irradiation of a surface is more uniform the greater the focus object distance This must not therefore be shortened too much It should however be noted that uniform irradiation of the surface of an object is not of prime importance On the contrary a method the so called sieve treatment which involves the uneven irradiation of the object surface has long been employed In sieve therapy the skin may be exposed to a dose of even 20 000 R instead of the customary 3 000 R provided unexposed areas are left on the skin to facilitate recovery from radiation damage It would hence be desirable when large anode or multifocus tubes are constructed to find a solution that would make it possible to bring an anode fitted with beam collimators in contact with the object surface and in this way to apply short distance roentgen treatment with a sieve This presupposes that the electrons strike the anode from behind and the produced radiation passes through the

In practice this limits the magnitude of the peak angle

2 The penumbra can be reduced to moderate size It is demonstrated in Fig 2a that when the 'peak angle of the penumbra is $2a$ and p is its width at depth OT, then

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Also, the reduction of the penumbra requires a suppression of the peak angle

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$$\frac{\pi R_T^2}{\pi R_O^2}$$

may be called the geometric factor GF, the intensity of the radiation increases with distance in proportion to this ratio

$$\frac{R_O}{FO}=\text{tang}\ a \quad \text{and} \quad \frac{R_T}{FT}=\text{tang}\ a$$

and hence

$$\frac{R_O}{FO}=\frac{R_T}{FT} \quad \text{and} \quad \frac{R_T}{R_O}=\frac{FT}{FO}$$

regardless of the magnitude of the angle a, and

$$GF=\frac{\pi R_T^2}{\pi R_O^2}=\left(\frac{FT}{FO}\right)^2$$

Superposition of the conical beams thus leads to a geometric increase in the *radiation intensity which is proportional to the square of the ratio of FT to FO* On the other hand, eq (1), divergence of the conical beams produces a converse change in the radiation intensity according to the inverse square law This decrease in intensity is also proportional to the square of the ratio of these same distances

These two changes in intensity thus cancel each other the distances lose their significance, and the intensity diminishes as in parallel radiation only owing to absorption and secondary scattering radiation

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— Anode for a source of roentgen radiation (1965) (Application No 933 for patent in Finland)

MOON R J Amplification of the fluoroscopic image Amer J Roentgenol 59 (1948) 886

WITTE ZIMMER und KESSLER Ein neues Rontgenrohr zur Erzeugung konvergenter Strahlenbundel Fortschr Rontgenstr 60 (1939)

anode, and further that the anode be earthed, very thin and effectively cooled. The possibility of constructing a roentgen source of this type, and the advantages attainable by making the anode slightly convex or concave, will be discussed in a forthcoming publication.

When calculations are made to determine the usefulness of a large anode it should be remembered that many factors make it necessary to check the results by means of measurements in phantoms. The average thickness of matter penetrated by the radiation is slightly greater than the perpendicular distance from the surface to the depth in question. The outline of every radiation beam is also rendered indistinct by a focus of large area, even collimators made of heavy metal transmit some radiation and secondary radiation is produced at their edges, especially when high energy radiation is employed. These factors are under investigation.

It would be interesting to know whether the geometric factors discussed are of value with very high energy photon sources, such as the betatron and the linear accelerator. The radiation beams of these are narrow (~ 10°) and no collimator would be required when targets of large area are irradiated by moving the electron beam. When irradiation takes place with an energy source such as radium or cobalt 60, collimation would hardly be possible in practice owing to the thickness that would be required for the wall of the collimator.

SUMMARY

The possibilities of using radiation sources with anodes of large area in radiation therapy are explored. It is concluded that the focus object distance can be greatly reduced without influencing the per cent depth dose if the radiation is divided into a number of collimated beams.

ZUSAMMENFASSUNG

Die Anwendbarkeit in der Strahlentherapie von Strahlenquellen mit grossen Anodenoberflächen wird erörtert und es wird festgestellt dass ohne Einwirkung auf die relative Tiefendosis der Fokus-Hautabstand stark reduziert werden kann, wenn die Bestrahlung in mehreren Strahlenbündeln verteilt wird.

RÉSUMÉ

L'auteur a étudié la possibilité d'utiliser des sources de radiation ayant des anodes de grande surface en radiothérapie. Il conclut qu'on peut réduire beaucoup la distance foyer-objet sans influer sur le pourcentage des doses en profondeur à condition que le rayonnement soit divisé en plusieurs faisceaux collimatés.

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FROM THE GUSTAF WERNER INSTITUTE, UNIVERSITY OF UPPSALA AND THE DEPARTMENT OF RADIOTHERAPY, UNIVERSITY OF GOTHENBURG, SWEDEN

ROENTGEN STAND FOR FIELD POSITIONING IN HIGH ENERGY RADIOTHERAPY

by

BO JUNG, BÖRJE LARSSON, BENGT ROSENGREN, KAY STÅHL and WILHELM WRETLIND

The application of high energy radiation in external therapy has emphasized the importance of accuracy in the dose planning. The experience is that roentgenography with diagnostic stands is generally not adequate as a basis for the positioning of the radiation fields. This is mainly due to the fact that the actual projections and the proper focus to tumour distances are not achieved and there is also the trivial problem of having the patient positioned identically as on the therapy couch.

The high energy beams themselves are not suited for radiography due to the low contrast of the image. JOHNS & CUNNINGHAM (1959) introduced an auxiliary diagnostic roentgen tube in the therapy head, but such a system does not allow the therapy equipment to be fully utilized for irradiation. In recent years the construction of roentgen stands especially designed for field positioning and tumour localization has been undertaken at several radiotherapeutic centres (cf. below). This paper describes such a project. It has resulted in two, almost identical equipments which are now in use in Uppsala and in Gothenburg.

Submitted for publication 19 February 1968.

A The therapeutic procedure and the positioning stand

The construction principles and the use of a localization stand is probably best discussed with reference to the envisaged treatment procedure This is given by the following scheme

I Localize the outlines of tumour and internal organs in one or several parallel projections mark the projections of points of interest on the skin of the patient measure the outline of the patient and make with the aid of the skin marks accurate drawings of the desired cross-sections of the patient with tumour and internal organs indicated at proper positions

II Select treatment technique from information on position of tumour and critical organs as well as on possible earlier radiotherapy

III Calculate dose distribution

IV Simulate selected treatment fields check that the treatment fields are in correct position in relation to the target volume and the critical organs mark on the skin of the patient entrance (and exit) points of central beam axes and entrance (and exit) fields

V Adjust patient to therapy beam by aid of skin marks irradiate

From this scheme the following conclusions can be drawn regarding the specifications which should be met by the localization stand

1 Any projection which can be achieved with the therapeutic stands should be obtained In practice this condition prescribes a full 4π rotation with respect to the patient The movements available in the patient s couch decrease the requirements on the localization stand however

2 The focus-isocentrum distances should be variable and match those available in the therapeutic apparatus

3 The roentgen image should be transmitted by an image intensifier closed circuit TV system The image plane should be variable with respect to the patient so that the best image quality is secured Provisions for exposure of documentary roentgenograms should be made

4 The patient s couch including fixation apparatus rolls etc should match closely the one used at the therapeutic apparatus The movements of the couches do not necessarily have to be identical however

5 If the patient s posture can be accurately related to some external coordinate system it is possible to transfer the coordinates of the target volume at the localization stand to the therapeutic unit In this case the coordinate system should parallel exactly that of the therapy unit Usually transfer of patient coordinates from the localization stand to the therapy unit prescribes the use of castings and fixture or special stereotaxic apparatus

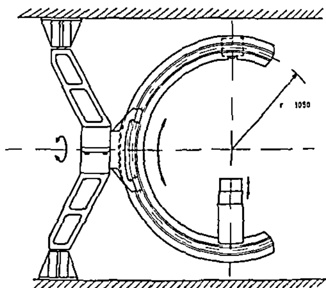


Fig 1 Early version of the localization stand employing a sliding and rotatory arc A 1 100 model was tested for mechanical and practical properties The advantages of this construction over the finally adopted principle are outweighed by the much higher manufacturing costs

6 When moving field therapy is important, the movements of the localization stand and the therapy units should match each other closely, also with respect to accuracy

7 The required accuracy depends critically on the intended use of the roentgen stand For localization and field control the demands are moderate, while for simulation of moving field therapy they are much higher If the faculty of accurate transfer of coordinates from the localization stand to the therapy equipment is requested the specifications for accuracy are even higher

Two approaches of marked different complexity have been followed in the development of roentgen stands for field positioning and simulation In the first the movement of the roentgen tube is restricted to a rotation around one axis in the other the roentgen tube (and image plane) has so many degrees of freedom that complete simulation of sophisticated therapy equipment is attained Examples of the first type are the constructions of BECKER, WERNER & WEITZEL (1955), CATTON (1957) FARMER, FOWLER & HAGGITH (1963) HEINZEL & WICHMANN (1963) and GREENE, NELSON & GIBB (1964) while NETTELAND (1967) and MADSEN (1967) have constructed apparatus of much higher flexibility

No detailed report of clinical experience is available for any of the constructions and it is hard to judge the importance of the various constructional features Most probably, the routine uses of the different stands will vary considerably from clinic to clinic depending on the local praxis and the therapy units at hand

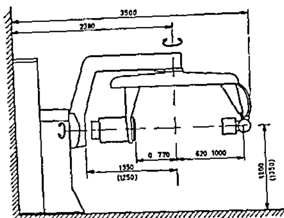


Fig 2 Localization stand with a rotatory arc on a rotatory arm This construction was finally adopted (The measures are in millimeters)

B Constructional

In a first model construction a combination of a rotation axis and a semi circular sliding action was tried (Fig 1) This construction may have some advantages with respect to the accessibility around the patient but was abandoned for technical and economical reasons

The final apparatus in Figs 2 and 3 employs a system of two intersecting orthogonal rotating axes and is related in principle to a diagnostic stand used in neuroradiology (FREDZELL & LINDGREN 1960) In conventional clinical praxis and when the patient s couch is mounted isocentrically one of the axes can be omitted but many therapy units have movements around two axes and a couch which is not mounted isocentrically This was the case with one cobalt unit and the betatron in Gothenburg Also as a localization stand for radiotherapy with high energy protons as in Uppsala both axes are necessary, since the direction of the proton beam is fixed in the room With this construction, projections with axes coincident with and perpendicular to the axes of the foreseen therapeutic beams are obtained without movement of the patient The extra complication of two axes is techniqually counterweighed at least partially by the fact that the movable arms carrying the roentgen source and the image amplifier can be made shorter without loss of accessibility to the patient The focus-isocentrum and image plane isocentrum distances are both variable Further degrees of free dom were considered unnecessary

The two rotary movements are driven by variable speed DC motors which also serve as brakes The translational movements of the roentgen tube and image amplifier are driven by a motor with constant speed In Uppsala the roentgen

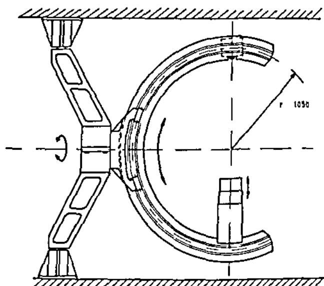


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D Practical experience

The Uppsala equipment now in use since several years has met the expectations very well It is used to align the patients for proton therapy and the most common projections are antiparallel and perpendicular to the beam The severe space limitations at the narrow irradiation site further accentuated by the necessary equipment for the proton beam has posed some access problems The experience gathered in Gothenburg over two years and from about 1 500 patients is of more general interest and is discussed in a paper subsequently to be published (JOHANSSON ROSENGREN & TJERNBERG) In routine work the equipment allows the patient s preparation for irradiation to be shortened by one day

Acknowledgements

The construction of localization stands for use in high energy radiotherapy has been the object of a discussion group formed within the Nordic Association of Radiophysicists We thank the members of the group and colleagues at our institutes for personal communications and practical advice The work was supported by Knut and Alice Wallenbergs Stiftelse the Swedish Medical Research Council and Elema Schonander

SUMMARY

A unit for use in dose planning and field localization with a roentgen source and an image amplifier mechanically coupled together by an arc is described The arc can be rotated isocentrically round two perpendicular axes The focus isocentrum and image plane isocentrum distances are both variable

ZUSAMMENFASSUNG

Ein Gerat fur Dosisplanung und Lokalisierung der Bestrahlungsfelder in dem die Rontgenquell und ein Bildverstarker durch einen Bogen mekanisch miteinander verbunden sind wird beschrieben Der Bogen kann isozentral um zwei perpendikulare Achsen rotiert werden Die Abstande Fokus Isozentrum und Bildebene Isozentrum sind beide variabel

RÉSUMÉ

Les auteurs décrivent un équipement destine a etablir le plan d irradiation et la localisation des champs au moyen d une source de rayons de roentgen et d un amplificateur d image réunis par un arc L arc peut tourner autour de deux axes perpendiculaires On peut faire varier la distance du foyer au centre de rotation et la distance du plan image au centre de rotation

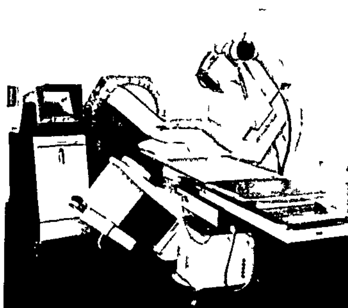


Fig 3 Localization stand at the radiotherapeutic clinic in Gothenburg The stand is now in routine use for localization and simulation during the preparatory procedures for radiotherapy with gamma and high energy roentgen rays

collimator is of conventional design (Siemens No 501 423), whereas in Gothenburg a special device which simulates the collimator systems of the therapy units has been used Four parallel bars outlining the margin of the field can be moved simultaneously in antiparallel directions and both pairs can be rotated together around the central axis of the roentgen beam

The image amplifiers are of Siemens make (10″ in Uppsala, 9″ in Gothenburg) coupled to Siemens closed circuit TV links whereas the roentgen sources are a Philips type PH 125/180 (max 125 kVp) in Uppsala and an Elema Schonander type Triplex Optimatic 723 (max 125 kVp) in Gothenburg The movement of the roentgen head is restricted to a little more than a hemisphere due to the inflexibility of the cabling for the roentgen and image intensifier equipments

The patient's couch is mounted isocentrically at both places It is important that the mounting of the couch does not interfere with the movements of the roentgen tube and image intensifier

C Precision

The Uppsala machine is the prototype and its isocentricity defined as the minimum volume crossed by a fixed line between the roentgen focus and the image plane for all settings of the equipment is of the order of 4 mm×4 mm×8 mm, the deviation being largest for horizontal settings of the arm The arm of the Gothenburg apparatus is 10 cm longer but has a more sturdy construction and the volume defined earlier is in this case 3 mm×5 mm×6 mm

FROM RADIUMHEMMET (DIRECTOR PROF J EINHORN) AND THE DEPARTMENT OF GYNECOLOGY (DIRECTOR PROF H L. KOTTMEIER), KAROLINSKA SJUKHUSET, STOCKHOLM SWEDEN

VASCULAR INSUFFICIENCY IN PREMALIGNANT AND PRE INVASIVE SQUAMOUS EPITHELIUM

by

L. RUBINSTEIN

The blood supply as well as the oxygen pressure are of great importance in malignant tumours treated by modern radiotherapy adequate circulation in the tumour tissues is also essential for positive therapeutic results in chemotherapy There is good reason to assume that the growing rate of many malignant tumours is much higher in the epithelium than in the underlying capillary bed This at an early stage often results in hypoxia leading finally to necrosis

Early investigations The importance of vascularization in the treatment of malignant tumours has been emphasized by CRAMER (1934) and MOTTRAM (1935) THOMLINSON & GRAY (1955) and GRAY (1961) studied the clinical application of the oxygen problem and correlated the morphologic and physiologic results Several papers on the morphology of the terminal capillary bed in the squamous epithelium present various correlations of the vascularization in early as well as advanced cases of carcinoma. The favourable anatomic site of the portio vaginalis uteri has rendered it popular for investigation and valuable results have already been obtained (SUGIHARA 1958 KOS et coll 1960 ZINSER & ROSENBAUER 1960 KOLLER 1963 KOS & LANE 1963 KOLSTAD 1964 1965 RUBINSTEIN 1968)

Submitted for publication 11 January 1968

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The blood supply as well as the oxygen pressure are of great importance in malignant tumours treated by modern radiotherapy adequate circulation in the tumour tissues is also essential for positive therapeutic results in chemotherapy There is good reason to assume that the growing rate of many malignant tumours is much higher in the epithelium than in the underlying capillary bed This at an early stage often results in hypoxia leading finally to necrosis

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These investigations indicate that the vascularization in the pathologically transformed squamous epithelium is different from that in normal epithelium The degree of vascular insufficiency in malignant tumours depends finally on the capillary circulation within the growth Even if oxygen therapy makes it possible in many cases to raise the partial oxygen pressure in the tumour and decrease the hypoxia, it is still difficult to achieve a uniform and general improvement of the circulation in the tissues This applies particularly to tumours with large inter capillary spaces, the increase in the capillary oxygen pressure obtained by oxygen *inhalation is not even sufficient to increase the oxygen pressure in intercapillary* tumour tissues (THOMLINSON & GRAY 1955, GRAY 1961) Information concerning the vascular conditions in the entire epithelium, and on the hypoxia that may occur in the intercapillary tissues is therefore of particular interest

The author has developed an optical method that offers authentic registration of the morphologic features of the epithelium and the underlying capillary bed (1956, 1967) The more marked the growth of the epithelium is, the coarser appears the capillary bed, and, at the same time, the greater is anemia The present paper deals with further development of this method, by means of which it is possible practically to study eventual correlations between the vascular insufficiency of the epithelium and the precancerous and pre invasive epithelial appearances

Material This is based on the investigation of 164 women in ages from 17 to 77 years The total number of squamous epithelial areas in the portio uteri investigated was *364* *Each portio was examined first by means of a cytologic* smear and then through a colposcope, in several cases with direct photographic recording of selected areas All the 364 specimens were examined histologically The findings were as follows

		Number of specimens
Inflammation only		185
Dysplasia		
of low degree	71	
of high degree	48	119
Carcinoma in situ		60

Author's method A self retaining speculum having been introduced into the vagina, the ectocervix is inspected and a cytologic smear taken from the vagina and the posterior vaginal fornix The portio is examined through the colposcope The mucous secretions are removed with physiologic saline and acetic acid 2 %



Macroscopic appearance of squamous epithelium hyperemic (top), hyperemic of low degree (middle) and hyperemic of high degree (bottom view)

is applied by soft gauze pressed on the epithelium, the epithelium is thus fixed in vivo. The cytologic smear is stained by the Papanicolaou original method (PAPANICOLAOU & TRAUT 1943). The histologic specimens are fixed in formalin, embedded in paraffin, and stained by the van Gieson and periodic acid Schiff methods.

The use of acetic acid 2 % plays the main role in this procedure. HINSELMANN (1938) pointed out the advantage of acetic acid 2 % to 4 % in so called enlargement colposcopy. GANSE (1958) and KOLSTAD (JOHANNISSON et coll. 1966) have been critical of the use of astringent solutions in the study of epithelium in vivo. They have pointed out that fine capillary networks disappear and coarse networks become coarser after such fixation. Taking the epithelium as a whole, the changes in the morphologic appearances produced by the acetic acid seem to me advantageous, however (RUBINSTEIN 1966, 1967). Fine normal capillaries are to some extent blurred out, whereas the coarse and pathologic capillaries appear more clearly. The contrasts thus become more accentuated, a fact that makes the evaluation easier. Numerous finer terminal capillaries appear clearly first after fixation, to disappear or to be blurred out again in 2 to 3 minutes. Further fixation causes the capillaries to re appear.

Normal vascular appearances. The epithelial regrowth in histologically normal regions may be examined by a colposcope, this takes place in the so called transformation zone that lies between the cylindrical and the squamous epithelium and consists of a narrow circular zone bounded on the two sides by indistinct borders. The characteristic structure of the cylindrical epithelium may be observed under the thin squamous epithelium. A red epithelial zone is first apparent but fixation causes the thin squamous epithelium to appear, and the underlying ectopic cylindric epithelium will be visible. The terminal capillaries consist of fine linear and network capillaries or fine circular and spider capillaries. Immediately after fixation the terminal capillaries are blurred out, and no atypical capillaries are visible.

Hyperemia. The hyperemic squamous epithelium in the portio is characteristic in appearance, the thin and transparent epithelium is intensely red and richly vascularized. When fixed in vivo the underlying capillary bed emerges as small and fine punctuations among network and circular capillaries. These punctuations often appear very clearly just after fixation, and lose their colour after some minutes. The epithelium as a whole is richly vascularized and intensely red in colour, it is always thin and elastic.

Hypemia. The hypemic squamous epithelium has a clear tendency towards proliferation, with marked variations in colour and thickness. The capillaries are

Table

Vascularization and histologic findings in 364 epithelial specimens

	Number of specimens	Inflammation only	Dysplasias Low degree	Dysplasias High degree	Carcinoma in situ
Normal vascularization	90	76	13	1	—
Hyperemia	21	11	9	1	—
Hypemia	253	98	49	46	60

coarse and variable in appearance coarse punctuations alternating with mosaic capillary zones the capillaries are dilated Due to poor vascularization and circulation the epithelium has an anemic grey or greyish white colour and keratinization may occur Advanced epithelial proliferation keratinization and coarse capillaries may be associated with a high degree of hypemia The intercapillary distances are increased

Results and Discussion

No epithelial area with normal capillary characteristics and vascularization presented histologic signs of carcinoma in situ There was one case of high-degree dysplasia (1 5 %) among the 90 cases in this group The number of low degree dysplasias were 13 (14 5 %)

No hyperemic epithelial area had evidence of carcinoma in situ High degree dysplasia was present in one of the 21 cases in this group (5 %) and low degree dysplasia was present in nine of the cases (43 %)

All the 60 cases of carcinoma in situ were found in the hypemic epithelium eries A similar hypemic vascularization was present in 96 % (46/48) of the high degree dysplasias and in 69 % (49/71) of the low degree dysplasias in this group

The existence of histologically benign inflammatory epithelium in all the three groups of vascularization proves that the vascular appearance of the epithelium is not a decisive criterion of malignancy

Valuable information on the circulation in the tumour is obtained by complementing the morphologic examination of the capillary beds with measurements of the oxygen pressure in the tumour and study of the variations before and during therapy Such measurements generally confirm the inadequate vascularization and hypoxia of a malignant tumour

Experiments in animals have indicated (THOMLINSON & GRAY 1955, and GRAY 1961) that the effect obtained for instance by oxygen inhalation does not include the more central parts of the tumour Complete anoxia, in spite of the partial oxygen pressure of the arterial blood, may exist at a distance of 0 2 mm from the terminal capillaries These observations are of paramount practical value because they offer an explanation of the fact that for many tumours oxygen therapy has no effect KOLSTAD (1964, 1965) proved that large intercapillary distances (>0 25 mm) produce a characteristic sign in malignant, pre invasive epithelium Even dysplastic epithelium often displays similar vascular characteristics

The epithelium as a whole may also be examined in order to obtain some idea concerning the circulation in precancerous or pre invasive epithelial change (RUBINSTEIN 1966, 1967) Then, not only the morphologic features of the capillary bed but also the colour, tendency to proliferation and the superficial structure of the epithelium are examined Typical findings indicating early malignant epithelial changes are marked vascular insufficiency and anemia The question of correlation between this vascular insufficiency and the degree of epithelial malignancy is of considerable importance The capillary changes may offer important information on the neoplastic activity of the epithelium but cannot be used as a *direct measure of malignancy The whole epithelium must be examined* Dysplasia and carcinoma in situ are histologic terms implying that a careful study of the various epithelial layers has been made, but has not necessarily included the underlying capillary bed

The various vascular appearances are optical images of the capillaries of the stromal papillae caused by the mutual activity between these capillaries and the finger like epithelial buds

The present material proves that the precancerous and pre invasive squamous epithelia are usually hypemic Furthermore, a hypemic epithelial area need not necessarily be malignant Malignant tumours are dynamical, kaleidoscopic growths The appearance of the epithelium is one co ordinate in the whole system, while the appearance of the capillaries is another Only occasionally do these two run parallel

SUMMARY

Characteristic hypemia was evident in precancerous and pre invasive tissue of the portio vaginalis uteri examined in vivo in a material of 164 subjects Changes in the epithelial appearance are correlated with vascular insufficiency of the epithelium The significance of the findings is discussed

ZUSAMMENFASSUNG

Bei in vivo Untersuchung der Portio vaginalis uteri in 164 Fallen wurde festgestellt dass eine stark verminderte Gefassversorgung ein characteristisches Zeichen von precancerosem Gewebe war Korrelation zwischen dem Aussehen des Epithels und der geringen Blutzufuhr zum Epithel wurde konstatiert Die Bedeutung dieser Befunde wird erortert

RÉSUMÉ

Sur une serie de 164 malades examinees in vivo l auteur a trouve une diminution caracteristique de la circulation dans les tissus precancereux et pre invasifs du col de l uterus Il a établi une corrélation entre les aspects épitheliaux et l insuffisance vasculaire de l epithélium L intérêt de cette constatation est etudie

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EVALUATION OF EXPERIMENTAL IRRADIATION FRACTIONATION WITH THE SINGLE HIT, MULTI TARGET MODEL

by

ERIK SPRING and PETER HOLMBERG

All theoretical models developed for indicating the dose response curve in irradiation of cells are based upon the interaction of ionizating radiation with the cells (FORSSELL 1924 WARREN 1957, HIGGINS 1958) The one most commonly used is the single hit multi target model (ZIMMER 1961) This model as represented by formula (1) is often referred to as a multi hit model although the equation does in fact correspond to a multi target model in which it is assumed that the cells have several targets each requiring one hit for inactivation This particular model was employed in this study The multi hit single target model (OLIVER & SHEPSTONE 1964) and the kinetic model (DIENES 1966) are also of value Some kind of treatment fractionation is usually applied in radiotherapy and consequently the function describing the total dose producing a certain effect for different numbers of fractions is of importance to radiotherapists Surveys of experimental findings concerned with the change in the total dose with fractionated treatment have been published (see FOWLER & STERN 1963 WOOTTON 1966) These findings were obtained in animal in vivo and in vitro experiments

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FOWLER (1965) presented two ways of considering the change in the total dose with the overall time used One way (A) was derived by replotting clinical data and results from normal tissues of experimental animals, it corresponded to a high extrapolation number and a survival curve slope that continued to increase with dose The other way (B) was by calculation from a simple cell survival model, assuming a single hit, multi target model with an extrapolation number of 2 8, and a 37 % dose slope D_0 = 140 rad He concluded that the two predictions may be regarded as limiting values between which the empirical answers might be expected to lie, although he preferred experimental results derived from (A)

If a start is made from the assumption that different types of radiosensitive and 'radioresistant cells exist at the beginning of the irradiation, or from the assumption that the cells change to more 'radioresistant' cells after several irradiations, a change is to be expected in the extrapolation number and in the 37 % dose slope during fractionation treatment The findings reported in this paper do not include cell repopulation during the time of treatment

The purpose of this study was to compare the results determined experimentally and reported by FOWLER (1965), and indicating the change in the total dose taken against the number of fractions, with corresponding results derived by means of the single hit, multi target model It was hoped that the use of a criterion in respect of the closeness of the fit of the experimental and theoretical results, together with a suitable assumption concerning a variation of the values of the extrapolation number and the 37 % dose slope, would permit a better description of the experimental results

The single hit, multi target model The fact that on the absorption of radiation, the events (hits) are statistically distributed and mutually independent means that Poisson's law is relevant If it is assumed that the cells consist of m targets, each of which must receive one hit to make the cell react, i e lose its reproductive integrity, the following formula is valid

$$S = 1 - (1 - e^{D/D})^m \qquad (1)$$

This formula gives the cell survival curve in dealing with the single hit, multi target model

S is the proportion of the cell population which survives the dose D (rad) D_0 (rad) is the 37 % dose slope, i e the dose required to reduce the survival proportion to 37 % of its initial value on the straight region of the logarithmic survival curve The extrapolation number m may be thought of as the average number of targets (sensitive sites) in the cell but should rather be regarded as a mathematical parameter with no morphologic or biochemical significance

It has been found that this formula provides a good description of the survival of a cell population given a single radiation dose Usually m lies between 2 and 10 and D_0 between 100 and 180 rad for oxygenated cells For anoxic cells D_0 increases to about 400 rad

Fractionation For small values of D the shoulder of the survival curve plays an important role In fractionation radiotherapy accordingly the total dose has to be increased for attainment of the same survival proportion as in one treatment this depends upon the reduction in the efficiency of irradiation with small doses The final surviving proportion S_N after N treatments may be calculated from the following formula

$$S_N=\{1-(1-e^{-D/ND_0})^m\}^N \quad (2)$$

assuming that parameters D_0 and m do not change during the fractionated treatment N is the number of fractions and consequently D/N the dose per fraction

The experimental values considered by FOWLER (1965) give the total doses D for different numbers of fractions 1 2, N If the doses given are used, then the same survival proportion S_N will be derived regardless of the number of fractions i e $S_1=S_2=$ $=S_N$ respectively If the experimentally determined values of D corresponding to different numbers of fractions are introduced into formula (2) a series of S_N are obtained all of which should be equal if the model describes the process perfectly, and the proper values for m and D_0 have been chosen This is not the case in practice, where a set of different S_N values results The values for these that best fit the experimental results are determinable by varying m and D_0 A general criterion called the relative closeness of fit has been employed this is indicated by Q and defined as follows

$$Q=\bar{S}^{-1}\{\Sigma(S_N-\bar{S})^2\}^{1/2}(k-2)^{-1/2} \quad (3)$$

$\bar{S}$ is the mean value of the S_N values obtained, S_N the survival proportion corresponding to N fractions and $(k-2)$ the degree of freedom where k is the number of experimental values

The smallest value of Q exhibits the best fit between the experimental and theoretical results The results of calculation are presented below

Cell population with two different cell types A model of a cell population comprising two different types of cells radiosensitive and radioresistant was also employed The following formula was used

$$S_N = x\{1-(1-e^{-D/ND_1})^{m_1}\}^N + (1-x)\{1-(1-e^{-D/ND_2})^{m_2}\}^N \tag{4}$$

x is the proportion of 'radiosensitive' cells at the beginning of the irradiation. Thus, $(1-x)$ is the proportion of the 'radioresistant' cells, D the total dose, N the number of fractions and D/N the dose per fraction as defined earlier. D_1 and D_2 are the 37 % dose slopes, and m_1 and m_2 the extrapolation numbers of the 'radiosensitive' and 'radioresistant' cells, respectively.

The criterion for closeness of fit given in formula (3) was also applied in the calculation with formula (4).

Cell population with varying parameters. A further model, in which parameters m and D_0 change during the fractionated treatment, was also studied. The formula corresponds to a cell population which changes to a more 'radioresistant' one with an increasing number of fractions.

$$S_N = \{1-(1-e^{-D/NA})^B\}^N \tag{5}$$

where

$$A = A_1-(A_1-150)N^{-c}$$

$$B = (\varepsilon-1.5)N^{-c}+1.5$$

A represents the 37 % dose slope which varies in accordance with the formula presented above. It is assumed that the 37 % dose slope is 150 rad at the first irradiation. This value holds good, at least approximately, in most cases where cells have been irradiated. During the fractionated irradiation, the value changes towards A_1, which has been assumed to lie between 250 and 450 rad. Exponent c determines the speed of the change, and if this is varied it might be possible to determine the speed. B represents the extrapolation number, defined by the formula presented above. Also here, c determines the speed of the change. ε is the extrapolation number at the first irradiation and changes towards 1.5. The value 1.5 was arrived at from the calculations in the next section.

The relative closeness of fit was also determined by means of formula (3).

Results and Discussion

In all the calculations, use was made of the experimental results published by FOWLER (1965), as shown in Fig. 6 and in the Table. The numerical calculations were effected with the Elliot 803 Computer at the Department of Theoretical Physics, University of Helsinki.

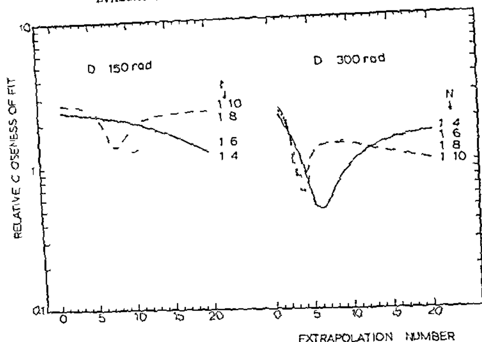


Fig 1 Results of calculations with formulas (2) and (3) N indicates the interval of fractions included in the calculations The curves depict results of the study of fractions from 1 to 10

As has been demonstrated by WOOTTON (1966), the change in the total dose D for five irradiations or more, can be expressed by the formula

$$D = D_1 N^a \qquad (6)$$

where N is the number of fractions and D the total dose needed in N fractions to arrive at the same survival proportion as for another irradiation number exceeding four D_1 is the extrapolated iso effect dose in one fraction and a is a constant characteristic of the tissue system

These facts led to the assumption that the theory would provide a better fit for the experimental results if account were taken only of the results between the eighth and the last irradiation Initially however all the experimental results were included in the calculations but subsequently the initial and subsequent parts of the fractionation results were examined separately

Formulas (2) and (3) were used At first D_0 was varied from 50 to 500 rad in steps of 50 rad and m from 1 to 20 in steps of 1 When Ω was near minimum it was examined more carefully by changing D_0 and m, in small steps in the

$$S_N = x\{1-(1-e^{-D/ND_1})^{m_1}\}^N + (1-x)\{1-(1-e^{-D/ND_2})^{m_2}\}^N \quad (4)$$

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where

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The relative closeness of fit was also determined by means of formula (3).

Results and Discussion

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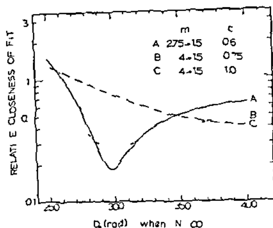


Fig 3 Results of calculations with formula (5) The minima at 300 rad show that the 37 dose slope changes from its initial value of 150 rad to about 300 rad The value of m and are indicated in the figure

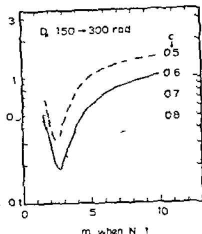


Fig 4 Calculations illustrating how the extrapolation number m changes between 2 and 4 to 1 5 when formula (5) is applied The value of D is indicated in the figure

m exceeds 2 at the beginning of irradiation and diminishes towards 1 6 during fractionation Nothing can be said about the dose slope D_0 from the results of calculations

If we start from the assumption that at the first irradiation $D_0 = 150$ rad, m is between 2 and 10 and the total dose is 2 000 rad (FOWLER) then after this irradiation the survival proportion will be $S = 0\ 3 \quad 1\ 6 \times 10^{-5}$ If it is assumed that $\lambda = 30$ i e 30 irradiations $m = 1\ 6$ and $D = 200$ rad per irradiation (FOWLER) there must be $D_0 = 280$ to 310 rad to arrive at the same survival proportion This involves a change in D_0 from 150 to about 300 rad

The calculations with application of formula (3) a mixture of two cell types did not provide any acceptable results In these calculations the radiosensitive cells were assumed to have the 37 % dose slope $D_1 = 150$ rad and the extrapolation number $m_1 = 2$ to 15 the radioresistant cells had $D_2 = 150$ to 450 rad and $m_2 = 1\ 6$ respectively The best results were obtained for $m_1 = 5$ to 8 and $D_2 = 300$ to 400 rad but the smallest value of Q was about 1 8 (This type of cell population does not seem useful in the application of the single hit multi target model)

Finally we employed formula (4) for a cell population in which the parameters change during the fractionated irradiation The starting assumption was that D_0 is 150 rad at the *first* irradiation and changes towards a higher value 250 to 400 rad with an increasing number of irradiations The values

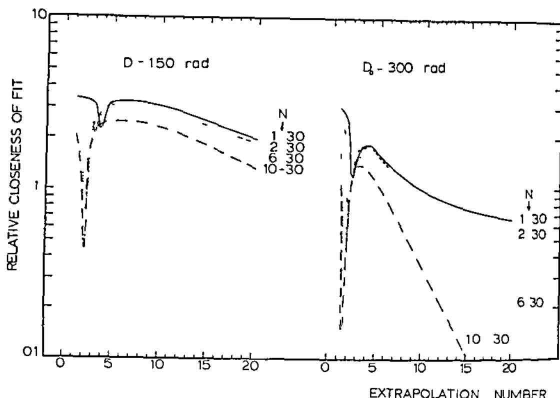


Fig 2 Results of calculations with formulas (2) and (3) on the study of fractions from 1 to 30 (Compare legend to fig 1)

region near the minimum The experimental dose D should produce the same S_N, regardless of the number of fractions The obtained quantity of Q should accordingly at its minimum give the values of D_0 and m that best describe the experimental results The results for $D_0=150$ rad and $D_0=300$ rad appear in Figs 1 and 2

It may be observed that, independently of D_0 the value of m moves towards a value of about 1 6 if the total doses D for small numbers of N are neglected This means that during the fractionation m falls from its initial value probably between 2 and 10 to about 1 6 This is discernible from the curves in which the calculations include N from 1 to 30 and from 10 to 30 Moreover the curves based on N values from 1 to 10 indicate that at the beginning of the treatment m is higher than 3 5 for $D_0=150$ rad, and higher than 2 for higher D_0 values The agreement between experiment and theory is usually better on an increase in D_0 It has been assumed that the minima at low m values are the realistic ones until experimental evidence in support of higher extrapolation numbers may be brought forward The final conclusion is that the extrapolation number

Table

Comparison of experimental and theoretical results

Number of fractions N	Experimental results FOWLER (1965) D_{total} (rad)	Theoretical results based upon the single hit multi target model				
		$D = 150$ rad, $m = 3\ 5$, $S = 4\ 50 \times 10$	$D = 300$ rad, $m = 1\ 6$, $S = 1\ 12 \times 10$	Formula (5) $c = 0\ 6$, $S = 5\ 44 \times 10$		
		D_{total} (rad)	D_{total} (rad)	D_{total} (rad)	D (rad)	m
30	6 000	6 240	6 000	6 030	281	1 6[illegible]
20	5 460±50	5 140	5 360	5 500	275	1 71
15	5 070±70	4 500	5 025	5 100	270	1 75
12	4 810±70	4 100	4 800	4 780	266	1 78
10	4 560±70	3 800	4 620	4 500	262	1 81
8	4 300±80	3 500	4 410	4 280	257	1 8[illegible]
6	4 010±80	3 170	4 220	3 940	249	1 93
4	3 490±120	2 830	3 920	3 500	235	2 04
2	2 730±160	2 475	3 690	2 780	201	2 33
1	2 000±250	2 265	3 555	1 970	150	2 75

The changes in the parameters are rather rapid and they may be considerable even after four irradiations as can be seen from the Table and Fig 6 in which the results of calculations are compared with the experimental findings of FOWLER Close agreement may be attained if the last model proposed in the form of formula (5), is applied

It would seem that the present findings should be taken into consideration in connection with fractionated irradiation of cell populations or in connection with fractionated radiotherapy

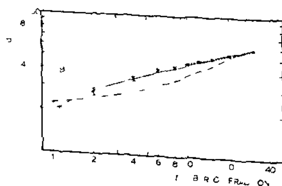


Fig 6 A comparison of experimental results (FOWLER 1965) with theoretical calculations Curve A is derived from formula (2) with $D = 150$ rad and $m = 3\ 5$ Curve B gives similar results with $D = 300$ rad and $m = 1\ 6$ Curve C is the best fit on application of formula (5) The values of the parameters D m and c are contained in the Table presented

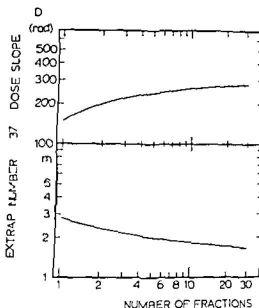


Fig 5 Curves showing the change in D_0 and m for the best fit obtained with formula (5)

used for m were from 1 5 to 15 at the first irradiation, these were allowed to change towards 1 5 The variation in both parameters was determined by the formula presented in the preceding section The results of calculations, some of them presented in Figs 3 and 4, indicate that the best agreement between theory and experiment, i e the smallest values of Ω, was arrived at on a change in D_0 from 150 to 300 rad, in m from 2 75 to 1 5, and to have $c=0\ 6$ The value of c is sharply determined, which means that the change in D_0 and m becomes apparent Fig 5 indicates the change in D_0 and m when $c=0\ 6$ The results should be so understood that for a definite number of fractions the values of D_0 and m are average values which correspond to that particular number of fractions In fact, the value of D_0 is less than that of the average value at the beginning of the fractionated irradiation, and larger in the later part Similarly when N irradiations are made, the value of m exceeds its average at the beginning, and is smaller at the end of the irradiations

In conclusion, the last model seems the best one for describing the change in the total dose during fractionated irradiations of cells It was assumed that during the irradiations the 37 % dose slope changes from its initial value o 150 rad to about 300 rad The extrapolation number has a value between 2 and 4 at the beginning, and changes towards about 1 5 at the end of the fractionated treatment

The results now arrived at seem to confirm the view that the radioresistance of irradiated cell populations may change during fractionated treatment

Table

Comparison of experimental and theoretical results

Number of fractions N	Experimental results FOWLER (1965) D_{total} (rad)	Theoretical results based upon the single hit multi target model				
		$D = 150$ rad, $m = 3.5$, $S = 4.50 \times 10$	$D = 300$ rad, $m = 1.6$, $S = 1.12 \times 10^{-4}$	Formula (5) $\varepsilon = 0.6$, $S = 5.44 \times 10$		
		D_{total} (rad)	D_{total} (rad)	D_{total} (rad)	D (rad)	m
30	6 000	6 240	6 000	6 030	281	1 66
20	5 460±50	5 140	5 360	5 500	275	1 71
15	5 070±70	4 500	5 025	5 100	270	1 75
12	4 810±70	4 100	4 800	4 780	266	1 78
10	4 560±70	3 800	4 670	4 500	262	1 81
8	4 300±80	3 500	4 410	4 280	257	1 86
6	4 010±80	3 170	4 220	3 940	249	1 93
4	3 490±120	2 830	3 920	3 500	235	2 04
2	2 730±160	2 475	3 690	2 780	201	2 33
1	2 000±250	2 265	3 555	1 970	150	2 75

The changes in the parameters are rather rapid and they may be considerable even after four irradiations as can be seen from the Table and Fig 6, in which the results of calculations are compared with the experimental findings of FOWLER Close agreement may be attained if the last model, proposed in the form of formula (5) is applied

It would seem that the present findings should be taken into consideration in connection with fractionated irradiation of cell populations or in connection with fractionated radiotherapy

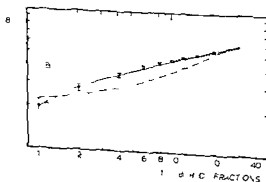


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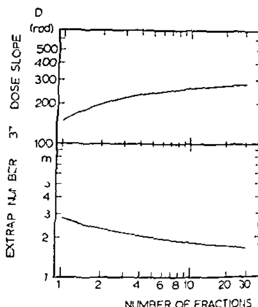


Fig 5 Curves showing the change in D_0 and m for the best fit obtained with formula (5)

used for m were from 1 5 to 15 at the first irradiation, these were allowed to change towards 1 5 The variation in both parameters was determined by the formula presented in the preceding section The results of calculations, some of them presented in Figs 3 and 4, indicate that the best agreement between theory and experiment, i e the smallest values of Q, was arrived at on a change in D_0 from 150 to 300 rad in m from 2 75 to 1 5, and to have $c=0$ 6 The value of c is sharply determined, which means that the change in D_0 and m becomes apparent Fig 5 indicates the change in D_0 and m when $c=0$ 6 The results should be so understood that for a definite number of fractions the values of D_0 and m are average values which correspond to that particular number of fractions In fact, the value of D_0 is less than that of the average value at the beginning of the fractionated irradiation, and larger in the later part Similarly when N irradiations are made, the value of m exceeds its average at the beginning, and is smaller at the end of the irradiations

In conclusion, the last model seems the best one for describing the change in the total dose during fractionated irradiations of cells It was assumed that during the irradiations the 37 % dose slope changes from its initial value o 150 rad to about 300 rad The extrapolation number has a value between 2 and 4 at the beginning, and changes towards about 1 5 at the end of the fractionated treatment

The results now arrived at seem to confirm the view that the radioresistance of irradiated cell populations may change during fractionated treatment

FROM THE RADIUM CENTRE (DIRECTOR P. BJERRE HANSEN), COUNTY AND CITY HOSPITAL, ODENSE, DENMARK

LATE RESULTS FOLLOWING RADIOTHERAPY OF SKIN CANCER

by

P. BJERRE HANSEN and M. SCHARLING JENSEN

Radiotherapy of carcinoma of the skin was first tried in 1899 and has for the last half century been acknowledged as an effective and comparatively non-injurious method of treatment. The application of radium was the method of choice in the first decades but during the last twenty years or so low voltage roentgen therapy has predominated.

The literature regarding radiotherapy of carcinoma of the skin is extensive and includes so many comprehensive Scandinavian contributions that an adequate impression of the development in this field may be obtained by reference to the publications of NORDENTOFT (1914), COLLIN (1928), NIELSEN (1933, 1951), MAGNUSSON (1935), EBBEHØJ (1936—1951), HULTBERG (1943), MOSEKILDE (1951), SCHMIDT & ANDRUP (1953), KVORNING (1959), JOHANSEN (1961) and JENSEN (1965). Radium treatment was the main theme of the earlier studies with EBBEHØJ, HULTBERG, and later investigators concerned themselves mainly with roentgen therapy.

The results of radiotherapy of carcinoma of the skin are in the majority of studies assessed as survival rates after 5 years observation. This survival criterion

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SUMMARY

The experimental results of FOWLER (1965) of the change in the total dose with an increasing number of irradiations of cells have been compared with theoretical calculations based upon the single hit, multi target model

ZUSAMMENFASSUNG

Die experimentellen Untersuchungen von FOWLER (1965) uber die Veranderung der Totaldosis mit zunehmender Anzahl fraktionierter Bestrahlungen von Zellen wurden mit theoretischen Berechnungen verglichen die auf Basis der Treffertheorie mit einem single hit multi target Modell durchgefuhrt wurden B

RÉSUMÉ

Les résultats expérimentaux de FOWLER (1965) sur la modification de la dose totale quand on augmente le nombre des irradiations des cellules ont été comparés avec les calculs théoriques basés sur le modèle du coup unique à cible multiple

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Table 1 *(cont.)*

Radium puncture			
<100	100–300	>300	Total
39	28	13	80
31	25	11	67
8	3	2	13
79 5	89 3	84 6	83 7
25	17	9	51
20	15	8	43
5	2	1	8
80	(88 2)	(88 9)	84 3

flat boxes or moulages, or inserted in needle shaped radium containers at intervals of 5 mm into the tumour tissue respectively The radiation dose has been expressed as the product of the amount of radium used in milligrams and the treatment time in hours i e mgh

The dose was between 700 and 1 200 mgh in almost 150 cases of contact therapy This corresponds to a dose of between 100 and 150 mgh/cm to the field of treatment i e the tumour surface which has rarely measured more than 5 to 6 cm plus a safety margin of about 1 cm and to an approximated tumour dose of around 1 800 R at a depth of 5 mm The dose in 21 cases has been lower than 500 mgh corresponding to approximately 50 to 80 mgh/cm and a tumour dose around 1 000 R at a depth of 5 mm

The radium contact treatment has resulted in freedom from recurrence in 71 5 % of all cases and in 73 8 % of the 107 cases observed for at least 10 years (Table 1) The frequency of recurrence in relation to the doses applied has been approximately 25 % after doses of around 700 to 800 mgh whilst recurrence has occurred in ten of the 21 cases in group I where the dose has been lower than 500 mgh These results are rather poor doubtless due to underdosage particularly in group I

The radium puncture treatment has been performed with from 2 to 7 needles loaded with 5 or 10 mg of radium and the period of treatment has most frequently been 4 to 5 hours The dose expressed in milligram hours has varied from 40 to 500 but has generally been between 80 and 200 mgh

Table 1 reveals that recurrence developed after radium puncture in thirteen

Table 1

Relationship between results and doses in radium treatment of skin cancer

Dose in mgh	Radium contact therapy			
	<500	500—1000	>1000	Total
Number of growths treated	21	107	72	200
= recurrences	11	80	52	143
+ recurrences	10	27	20	57
Freedom from recurrence %	52.4	74.8	72.3	71.5
Number of growths observed after treatment	11	65	31	107
= recurrences	6	49	24	79
+ recurrences	5	16	7	28
Freedom from recurrence	(54.5)	75.4	77.5	73.8

plays, however, a minor role in the evaluation of the results of treatment of skin cancer because the condition carries a very low mortality. This means that relatively large numbers of these carcinomas may be observed for as long periods as ten years or more after treatment.

Surveys with regard to the late results of radiotherapy of skin cancer, and of the cosmetic and functional results, are not very common (see, however, KVORNING 1959, and JENSEN 1965).

A total of 1 827 cases of skin cancer, referred for treatment to the Odense Radium Centre during the period 1937—1955 have been reviewed in an attempt to throw some light on these problems. A follow up study of the surviving 298 patients was carried out during 1965. A detailed survey of these studies was given to the University of Copenhagen in a special report (JENSEN). The various methods of irradiation used are now discussed in more detail in relation to the results obtained. The material has *for this purpose been limited* to 1 198 lesions definitely verified histologically as superficial epithelial carcinomas and primarily subjected to radiotherapy. It should be noted that epithelial carcinomas, localized to the lips and to the female and male genital regions, are not included since these differ clinically and therapeutically from other skin carcinomas.

Radium treatment of skin carcinoma. Radium treatment was frequently used until about 1943 but since then only occasionally. The treatment was given as 'contact therapy' in 200 cases and as 'radium puncture' in 80 cases. This mean application of radium sources on the surface of the tumour, either packed in

Table 2 *(cont)*

Treatment with 60 kV

1	1	2—4	5—7	8—15	Total
3 000	3 000—5 000	1 000—3 000	500—1 00	300— 500	
3 000	4 000	5 000	3 500—5 000	4 000—4 500	
2 000	2 600	3 300	2 800	2 700	
213	138	103	148	83	685
18	120	93	122	50	567
31	18	10	26	33	118
85 4	87	90 3	82 5	60 3	82 8
83	58	38	72	53	304
70	52	35	57	29	243
13	6	3	15	24	61
84 2	89 6	92	79 2	54 7	79 9
125	83	58	73	24	363
103	71	50	57	17	298
22	12	8	16	7	65
82 4	85 6	86 2	78 4	70 8	82 1

Finally it should be mentioned that other methods of radium treatment and combined roentgen and radium therapy have been used primarily in a further 32 cases This group is not registered in the tables

Roentgen therapy of skin cancer Roentgen therapy has been given throughout the 19 year period as soft radiation with a beam quality corresponding to half value layers (HVL) in skin from 6 to 10 mm (685 cases) or since 1950 with ultra soft roentgen rays with a HVL in skin of approximately 2 mm (163 cases) The two types of roentgen radiation correspond with regard to voltage filament current filtration and focus-skin distance to 60 kV 15 mA 0 4 to 0 5 mm Al and 3 to 7 cm and 30 kV 15 mA 0 2 mm Al and 10 cm respectively They will in the following be referred to as 60 kV and 30 kV Both have been given either as a single (one sitting) treatment with doses in air of from 3 000 to

Table 2 7

Relationship between results and doses in roentgen treatment of skin cancer

Treatment with 30 kV					
Number of treatments	1	1	2—4	4—7	Total
Single dose (R in air)	3 000	3 000—5 000	1 000—3 000	500—1 000	
Mean total dose (R in air)	2 800—3 000	4 200	3 000—4 000	3 500—4 500	
Mean tumor dose[1]	1 800—2 000	2 800	2 400	2 600	
Number of growths treated	33	57	50	23	163
= Recurrences	23	52	40	20	135
+ Recurrences	10	5	10	3	28
Freedom from recurrence	70	91 2 %	80	87 %	82 8 %
Number of spinocellular and mixed carcinomas	10	13	13	6	42
= Recurrences	7	11	9	5	32
+ Recurrences	3	2	4	1	10
Freedom from recurrence	7/10	11/13	9/13	5/6	76 2 %
Number of growths observed > 10 years after treatment	13	33	34	13	93
= Recurrences	8	31	26	11	76
+ Recurrences	5	2	8	2	17
Freedom from recurrence	8/13	94 %	76 5	11/13	81 7

[1] At 1 5 mm depth for 30 kV and 5 mm depth for 60 kV

of the 80 cases and in eight of the 51 cases observed for 10 years or more This gives a cure rate of approximately 84 % in both groups The results following radium puncture are thus somewhat better than those after contact treatment This difference is statistically significant, as p is less than 0 05

A calculation of the exact tumour dose in the various cases is not possible because information regarding the true dimensions of the tumours and the detailed positioning of the radium needles is inadequate An average estimation suggests however that the tumour dose in the majority of cases has been of the order of magnitude around 2 500 R at a distance of 5 mm from the radium sources

Contact therapy, because of the poor results, has been practically abandoned for treatment of skin cancer Radium puncture is almost exclusively limited to the treatment of lip cancer and urethral orifice carcinoma These are however as previously mentioned, not included in the present survey

Table 2 *(cont)*

Treatment with 60 kV

1	1	2—4	5—7	8—15	Total
3 000	3 000—5 000	1 000—3 000	500—1 00	300— 500	
3 000	4 000	*5 000*	*3 500—5 000*	*4 000—4 500*	
2 000	2 600	3 300	2 800	2 700	
213	138	103	148	83	685
187	120	93	122	50	567
31	18	10	26	33	118
85 4	87	90 3	82 5	60 3	82 8
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Relationship between results and doses in roentgen treatment of skin cancer

Treatment with 30 kV					
Number of treatments	*1*	*1*	*2—4*	*4—7*	Total
Single dose (R in air)	3 000	3 000—5 000	1 000—3 000	500—1 000	
Mean total dose (R in air)	2 800—3 000	4 200	3 000—4 000	3 500—4 500	
Mean tumor dose[1]	1 800—2 000	2 800	2 400	2 600	
Number of growths treated	33	57	50	23	163
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+ Recurrences	3	2	4	1	10
Freedom from recurrence	7/10	11/13	9/13	5/6	76.2 %
Number of growths observed ≥ 10 years after treatment	13	33	34	13	93
÷ Recurrences	8	31	26	11	76
+ Recurrences	5	2	8	2	17
Freedom from recurrence	8/13	94 %	76.5	11/13	81.7

[1] At 1.5 mm depth for 30 kV and 5 mm depth for 60 kV.

of the 80 cases and in eight of the 51 cases observed for 10 years or more. This gives a cure rate of approximately 84 % in both groups. The results following radium puncture are thus somewhat better than those after contact treatment. This difference is statistically significant, as p is less than 0.05.

A calculation of the exact tumour dose in the various cases is not possible because information regarding the true dimensions of the tumours and the detailed positioning of the radium needles is inadequate. An average estimation suggests however that the tumour dose in the majority of cases has been of the order of magnitude around 2 500 R at a distance of 5 mm from the radium sources.

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Table 2 (*cont*)

Treatment with 60 kV					
1	1	2—4	5—7	8—15	Total
3 000	3 000—5 000	1 000—3 000	500—1 00	300—[illegible]00	
3 000	4 000	5 000	3 500—5 000	4 000—4 [illegible]00	
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4 200 R, or as a fractionated treatment, consisting mainly in a course of 2 to 4 or 5 to 7 treatments in as many days, with daily doses of approximately 1 000 or 600 to 800 R, respectively (see Table 2)

The tumour doses cannot be calculated exactly because precise information regarding the dimensions of the mass and the size of the field in the vast majority of the cases is uncertain or lacking However, an attempt has been made to estimate the average magnitude of the tumour dose for each of the different groups treated (Table 2) It must be emphasized in this connection that a prerequisite for the use of 30 kV treatment is that the tumour tissue can be removed by scraping so that treatment field is flat and level, in order to ensure a uniform dose distribution, which is essential for the effectiveness of these soft roentgen rays Therapy at 30 kV can therefore be used only for the treatment of superficial tumours localized to smooth skin surfaces, and with a maximal diameter of 15 to 18 mm This means that the field of irradiation after scraping must not exceed 6 to 7 cm , including a safety zone of at least 5 mm around the tumour site

Therapy at 30 kV has been given as a one sitting treatment in 90 cases The dose in air has been between 2 500 and 3 000 R in 33 cases and approximately 4 200 R in 57 cases The results were considerably poorer in the first than in the second group as the recurrence rates were 30 % and 8 8 % respectively This difference is statistically significant ($0.001<p<0.01$) This was recognized in 1952, and the dose in air was accordingly increased to 4 200 R (corresponding to a tumour dose of approximately 2 800 R) This resulted in an improved cure rate around 93 % Incidentally the dose was later (1958) increased to 5 000 R (corresponding to a tumour dose of about 3 400 R) The majority of small skin carcinomas are still treated in this manner when the above mentioned requirements as to size and flatness of the field of treatment are complied with They are cured in about 95 % of cases

Therapy at 60 kV has been given as a one sitting treatment in 351 cases throughout the whole period, and has mainly been used for the treatment of growths with diameters up to between 20 and 25 mm and a thickness of up to between 5 and 6 mm The tumour dose has been approximately 2 000 R in 213 cases and about 2 600 R in 138 cases treated after 1952 The frequency of recurrence in the two groups has been 14 6 % and 13 % respectively, and for the cases observed for 10 years or longer it has been 17 6 % and 14 5 %

A cure rate of approximately 85 % is, however a somewhat poor outcome compared with the results obtained after 30 kV therapy given at one sitting with a tumour dose of approximately 2 800 R which in addition produces better cosmetic results Accordingly, the one sitting treatment with 60 kV has been abandoned

Fractionated irradiation has been used simultaneously with the one sitting treatment throughout the period as 60 kV treatment in 334 cases and as 30 kV treatment (1950—1953) in 73 cases The fractionation and doses are registered in Table 2 The most frequent procedure has been three to four, or five to six single treatments with doses in air of about 1 000 R or 600 to 800 R respectively given during a period of 6 to 8 days by the Strandquist scale

Fractionated 30 kV therapy was tried in an attempt to improve the cosmetic results but without success as the frequency of recurrence in these groups was as great as 13 to 20 % due to underdosage especially in the first of these two groups

Fractionated 60 kV treatment produced relatively good results after a tumour dose of about 3 300 R as there were only ten recurrences among the 103 cases in this group (9 7 %) The frequency of recurrence in the second group was 17.5 % presumably due to underdosage in a number of cases as the average tumour dose in this group was only about 2 800 R In the third group there were recurrences in thirty three of 83 cases (40 %) and in seven of the 24 cases followed for 10 years or longer This drop-out rate within the 10 years is unusually large This as well as the bad results may certainly be explained by the fact that this group included several large tumours a number of which should have been treated either with more penetrating radiation in larger doses or by operation

The indication for fractionated 60 kV treatment has been and is a skin carcinoma of irregular form and situated on an uneven surface with an area between 7 and 8 cm and a maximum thickness of 6 to 8 mm The total dose at the surface should preferably be about 5 600 to 6 000 R

A total of 848 carcinomas of the skin have been treated with soft and ultra soft roentgen rays in the various ways mentioned Recurrences have developed in 146 of these cases corresponding to a primary cure rate of 82 8 % Of 456 cases observed for more than 10 years after treatment 374 remained free from recurrence corresponding to a 10-year cure rate of 82 %

Finally roentgen therapy at 100 kV and 165—185 kV has been used as primary treatment in 34 cases of large growths Recurrence developed in sixteen of these cases This group is not registered in the tables

Frequency and treatment of recurrences Radiotherapy of the 1 198 cases of carcinoma of the skin has resulted in initial cure in a total of 955 cases Twelve patients died because of progressive tumour growth and metastases despite treatment In the remaining 231 cases local recurrences developed during the first year in 133 cases (57 %) and in 203 cases (88 %) less than 5 years after the first treatment The longest latent period was 19 years (2 cases)

4 200 R, or as a fractionated treatment, consisting mainly in a course of 2 to 4 or 5 to 7 treatments in as many days, with daily doses of approximately 1 000 or 600 to 800 R, respectively (see Table 2)

The tumour doses cannot be calculated exactly because precise information regarding the dimensions of the mass and the size of the field in the vast majority of the cases is uncertain or lacking However, an attempt has been made to estimate the average magnitude of the tumour dose for each of the different groups treated (Table 2) *It must be emphasized in this connection that a pre* requisite for the use of 30 kV treatment is that the tumour tissue can be removed by scraping so that treatment field is flat and level, in order to ensure a uniform dose distribution, which is essential for the effectiveness of these soft roentgen rays Therapy at 30 kV can therefore be used only for the treatment of super ficial tumours *localized to smooth skin surfaces, and with a maximal diameter of* 15 to 18 mm This means that the field of irradiation after scraping must not exceed 6 to 7 cm^2, including a safety zone of at least 5 mm around the tumour site

Therapy at 30 kV has been given as a one sitting treatment in 90 cases The dose in air has been between 2 500 and 3 000 R in 33 cases and approximately 4 200 R in 57 cases The results were considerably poorer in the first than in the second group as the recurrence rates were 30 % and 8 8 %, respectively This difference is statistically significant ($0\,001<p<0\,01$) This was recognized in 1952, and the dose in air was accordingly increased to 4 200 R (corresponding to a tumour dose of approximately 2 800 R) This resulted in an improved cure rate around 93 % Incidentally the dose was later (1958) increased to 5 000 R (corresponding to a tumour dose of about 3 400 R) The majority of small skin carcinomas are still treated in this manner when the above mentioned requirements as to size and flatness of the field of treatment, are complied with They are cured in about 95 % of cases

Therapy at 60 kV has been given as a one sitting treatment in 351 cases throughout the whole period, and has mainly been used for the treatment of growths with diameters up to between 20 and 25 mm and a thickness of up to between 5 and 6 mm The tumour dose has been approximately 2 000 R in 213 cases and about 2 600 R in 138 cases treated after 1952 The frequency of recur rence in the two groups has been 14 6 % and 13 %, respectively, and for the cases observed for 10 years or longer it has been 17 6 % and 14 5 %

A cure rate of approximately 85 % is, however a somewhat poor outcome compared with the results obtained after 30 kV therapy given at one sitting with a tumour dose of approximately 2 800 R which in addition produces better cos metic results Accordingly, *the one sitting treatment with 60 kV has been aban* doned

40 and 17 cases respectively and in a few cases this occurred up to eight times Nineteen of these 90 patients died from progressive growth and dissemination Seven patients died from other causes although with a verified and untreated local recurrence of the carcinoma of the skin No further recurrences have been observed so far in the remaining 64 cases

Lethal course and metastases Carcinoma of the skin was the cause of death of 46 patients i e 3 8 % of the 1 198 cases treated primarily with radiotherapy Twenty six of these died within the first 1 to 2 years after the first treatment and a further thirteen died during the following 3 year period Of the remaining 7 patients six died between 5 and 10 years and one patient died 17 years after the initial treatment The average age of the patients at death was 70 years and varied between 38 and 93 years Thirty two of these 46 patients were men and fourteen women This male predominance in mortality reflects mainly the previous observation that carcinomas of the ears are about three times as common in men than in women and have a recurrence rate of about twice the average and a mortality rate of 13 5 % compared with the average of 3 8 %

The total number of cases of ear carcinomas was 111 eighty four of which were men and twenty seven women The course was lethal in 15 cases (2 women and 13 men) In fourteen of these, the tumours were spinocellular or mixed carcinomas and metastases were verified in ten of these cases The patient with a basocellular carcinoma a man died due to invasion of the cerebrum

Carcinomas of the skin of the lower extremities have also presented a high mortality rate These tumours were mainly of the spinocellular type and caused the death of three patients out of 23 (13 %) Of 85 cases of eyelid carcinomas on the other hand 63 of which were of the basocellular type only three proved fatal (3 5 %) These three tumours were all spinocellular or mixed carcinomas

This difference with regard to the lethality between ear and eyelid carcinomas which have both had recurrence rates after radiotherapy twice as great as the majority of other malignant skin conditions emphasizes the suggestion that the local effect of radiotherapy is more dependent on factors such as localization and tumour size than on the histologic type of cancers of the skin On the other hand however the spinocellular and mixed carcinomas produce a far greater mortality than the basocellular carcinomas due to the fact that the spinocellular tumours produce metastases quite readily whilst the basocellular carcinomas rarely or never do so The histologic tumour type thus bears a considerable influence on the final results of radiotherapy of carcinoma of the skin

No cases of metastases were evident among the 700 cases of basocellular carcinomas reviewed and a lethal course was evident only in the three cases already discussed i e approximately 4 5 ‰ The remaining 43 deaths were caused by

An extraordinary recurrence rate has been found for carcinomas of the skin of the ears and eyelids, and of the lower extremities Of all the primary tumours 9 7 %, 6 7 % and 2 1 % were situated in the ears and eyelids and in the skin of the legs, whilst approximately 15 6 %, 9 1 % and 4 1 %, respectively, of all recurrences were within these regions The poor results of radiotherapy of carcinomas of the skin in these regions, as expressed by this high recurrence rate, are presumably due to the influence of such factors as poor vascularization and necrotic changes in the underlying cartilage or periosteum, either primarily or as a result of the radiation, through which the effect of the radiation on the tumour is diminished Geometrical and technical difficulties, especially met with in the treatment of carcinomas of the ears, may also sometimes have caused some underdosage

It must also be mentioned in this connection that about 75 % of the growths of ears and lower extremities have been spinocellular or mixed carcinomas, while only about 20 % have been basocellular carcinomas This predominance of spinocellular growths, which is the reverse of the figures for the distribution of the tumour types found in all other groups of skin carcinoma in this material was probably another factor of importance for the high recurrence rate in these two groups In the third group with a high recurrence rate, i e the growths of the eyelids, the basocellular carcinomas formed the dominant tumour type, however, and amounted to 70 % This observation, together with the finding that no distinct correlation existed between the treatment results, expressed as an initial freedom from recurrence, and the histologic types of tumour in the various groups, gives the impression that the local effect of radiotherapy is relatively independent of the histologic type of the tumour

These considerations lead to the conclusion, as emphasized by NIELSEN (1951), that carcinoma of the skin localized to these three regions, apart from very small lesions, should primarily be treated operatively This also applies to recurrent tumours in these regions During the last decade, repeat radiotherapy of skin carcinomas has been almost completely abandoned in favour of plastic surgery

The treatment of the 231 recurrent tumours in 197 cases of the present material, however, consisted in repeat roentgen therapy which was mainly given as fractionated 60 kV treatment Freedom of recurrence was obtained in only 102 of the cases (51 7 %) Surgical treatment resulted in an initial cure in twenty one of 26 cases, and electrocoagulation or local application of podophyllin was used with success in five of 8 cases Fifteen of these patients died from extension of growth and metastases following the first recurrence

In about two thirds of the remaining 90 cases the second relapse occurred less than one year after treatment of the recurrence After further treatment, which in most cases was roentgen therapy, a third and a fourth recurrence developed in

The subjective complaints and functional disorders consisted in 15 cases of itching in the scar (in some cases only after exposure to sunlight) and epiphora in 4 cases of carcinoma of the eyelid A reduction in sight occurred after treatment of the skin of the eyelid in 3 cases but this was marked only in a case treated with radium puncture in 1939

Of the 59 cases of recurrence, thirty six were cured after repeat roentgen treatment although in twenty two of these with comparatively poor cosmetic results Of the remaining twenty three cases surgical treatment gave acceptable cosmetic results in nineteen cases

Five of these patients complained of itching in the scar and two of epiphora One patient suffered from functional disturbances following a lower leg amputation and a younger woman developed an inferiority complex after an operative procedure resulting in some deformity of the nose The cosmetic results thus appear to be better after operative treatment than after repeat radiotherapy of recurrent carcinoma The groups are too small to permit of a definite evaluation but the results after the extended use of plastic surgery in later years have strongly confirmed this opinion On the whole, the cosmetic and functional side effects after irradiation of carcinoma of the skin have been comparatively slight and it is striking that so few of the patients have had any complaints

Conclusion

The methods and results of radiotherapy of a total of 1 198 cases of carcinoma of the skin treated in the period 1937—1955 have been surveyed and compared

Primary freedom from recurrence was obtained in 79 7 % of all the cases and in 83 6 % of the 647 cases observed for at least 10 years Recurrences developed after the first treatment in 243 cases but approximately 80 % of these were cured after repeat radiotherapy or other mainly surgical treatment The lethality of carcinoma of the skin in the 1 198 cases has thus been 3 8 %

The various methods of radiotherapy have given poor immediate results in several groups mainly because of underdosage Radium contact therapy has as a whole been insufficient as freedom from recurrence was recorded in only 7? % of these cases Radium puncture and fractionated 60 kV roentgen therapy in the groups with adequate dosage resulted in initial cure in close to 90 % of the cases The best results were obtained with 30 kV roentgen therapy in a single treatment with a dose of 4 200 R (in air) This procedure secured an initial cure of about 93 % of the tumours treated i e small superficial tumours

These results on the whole are slightly inferior to or on a par with other published results

JOHANSEN reported a five year cure rate as high as 96 % after fractionated

Table 3

Cosmetic results after radiation treatment of skin cancer

Follow up examination of 298 cases	Total	Appearance of scars Good	Fairly good	Disfiguring
Cases free from recurrence after first treatment	239	186 (77.8 %)	46 (19.2 %)	7 (3 %)
First treatment 30 kV 4 200 R × 1	24	21	3	0
First treatment 60 kV 3 000—5 000 R × 1	61	43	14	4
Cases free from recurrence after treatment of relapse	59	26 (44.1 %)	19 (32.2 %)	14 (23.7 %)
Radiotherapy of relapse	36	14	12	10
Surgical treatment of relapse	21	12	7	2

carcinomas of the spinocellular or mixed type, with verified metastases in twenty cases. As the material included almost 450 of these, the lethality was approximately 9.5 %.

Cosmetic and functional results. The cosmetic and functional results following radiation of carcinoma of the skin were evaluated in 1965 by a follow up examination of 298 cases of primarily irradiated skin cancers. Of these, 239 were cured by the initial treatment and the remaining 59 cases after repeat irradiation or other treatment.

The results of the evaluation are evident from Table 3 in which the appearances of the scars have been classified as good, fairly good or disfiguring. The objective changes that were considered were (1) depigmentation of the treated areas, (2) hyperpigmentation of the border zone, (3) atrophy of the epidermis and slight shrinking, (4) atrophy of the subcutis and loss of substance, (5) alopecia in regions covered with hair, (6) peeling or crust formation, and (7) occurrence of telangiectases in and around the scar. The scar was almost invisible in 41 of the 239 cases. In 145 cases there was moderate depigmentation and slight epidermal atrophy only. Marked depigmentation and hyperpigmentation together with moderate shrinking and telangiectases occurred in 46 cases. Loss of substance and considerable shrinking, crust formation, and marked telangiectases, in varying combinations, causing an unsightly and disfiguring scar had arisen in only 7 cases.

RÉSUMÉ

Les auteurs etudient differentes methodes de traitement par le radium et par les rayons de roentgen dans 1 198 cas de cancers cutanes verifies histologiquement au cours de la periode 1937—1955 Ils examinent en detail les resultats en particulier en ce qui concerne la guerison et les séquelles cosméthiques et fonctionnelles

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roentgen treatment of 334 skin carcinomas EBBLHOJ obtained freedom from recurrence in 96 2 % of 174 selected cases of small carcinomas with ultra soft roentgen irradiation (12 kV and 26 kV) MOSFKILDE similarly reported a cure rate of 90 4 % after treatment of 603 skin carcinomas with ultra soft roentgen therapy (one sitting, 26 kV) Freedom from recurrence occurred in 307 out of about 340 treated by HULTBERG with 30 kV and 60 kV therapy The results of radium therapy reported by COLLIN and by NIELSEN are on a par with the findings in this material, i e a relative cure rate of between 70 and 75 %

It has been demonstrated that radiotherapy to skin carcinoma must be given in doses of at least 4 200 R (in air) as a one sitting treatment with 30 kV to small growths, and with a total dose of about 5 600 R (in air) when fractionated 60 kV therapy is used in the treatment of larger skin tumours

Carcinomas of the skin of the ears, eyelids and lower extremities have twice as high a recurrence rate as in other sites This seems to be due mainly to complicating factors of anatomical and technical origin Furthermore, the growths in the ears and the lower extremities which in 75 to 80 % of cases have been carcinomas of the spinocellular or mixed type, have possessed a high tendency to produce metastases and accordingly have had a high mortality rate, 9 5 % against the average 3 8 %

These findings lead to the conclusion that the preferable treatment of skin carcinomas of the ear lower extremities and maybe the eyelids excepting very small tumours, appears to be plastic surgery rather than radiotherapy This also applies to the majority of all recurrent skin carcinomas after initial radiotherapy, since the survival rate and the cosmetic results after repeat radiotherapy is poorer than after surgery

The cosmetic results after one course of radiation treatment of carcinomas of the skin have on the whole been quite satisfactory inasmuch as disfiguring scars itching tenderness and malfunction have been observed only in a small percentage of cases

SUMMARY

Various methods of radium treatment and roentgen therapy in 1 198 cases of histologically verified carcinomas of the skin during the period 1937—1955 are discussed The results particularly as regards the cure rate and cosmetic and functional sequelae are considered *in detail*

ZUSAMMENFASSUNG

Ein Material von 1 198 Fallen von Hautkarzinom die mit verschiedenen Methoden von Rontgenbestrahlung und Radiumtherapie behandelt wurden wird kritisch besprochen Die Resultate wurden nicht nur mit Hinsicht auf Behandlungserfolge sondern auch auf die kosmetischen und funktionellen Erfolge eingehend ausgewertet

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EFFECTS OF SMALL DOSES OF RADIOACTIVE STRONTIUM ON THE RAT BONE MARROW

by

T STOKKE P OFTEDAL and A PAPPAS

Exposure of bone marrow to ionizing radiation will reduce its number of haematopoietic cells The cell reduction and subsequent regeneration following external irradiation has been studied experimentally as well as clinically The effect of irradiation from internal sources is to a great extent similar to that of protracted external total body irradiation with the same dosage (ALEKSANDROVA & SELIVANOVA 1963) and will be determined by several factors, such as the metabolic features of the radionuclide the quality of the radiation and the total radiation dose

In most of the experimental work recorded in the literature relatively large doses of radioactive substances were administered, and the reaction of the bone marrow could easily be observed in histologic sections The effects of small doses are more difficult to demonstrate and our present knowledge on this subject is rather scanty

The cell number of rat bone marrow was reduced for about 3 months following single injections of • Sr in amounts of 0 1 pCi/g As the radiation dose rate

From Norsk Hydro s Institute for Cancer Research the Norwegian Radium Hospital and the Division of Nuclear Chemistry University of Oslo Norway Submitted for publication 20 March 1968

STRAHLENSCHUTZ IN FORSCHUNG UND PRAXIS Band 7 Jahrbuch der Vereinigung deutscher Strahlenschutzärzte Herausgegeben von H R Beck, W Frik H Keim und H Braun 343 Seiten 4 farbige Abbildungen 32 Abbildungen 129 Zeichnungen 29 Tabelle Rombach, Freiburg i Br 1967 Preis 78 DM

This is a collection of lectures given during a course at Freiburg West Germany in October 1966 Most of the papers are centered on three main themes the first being the protection of the patient as well as the personnel and third parties against unnecessary radiation in diagnostic roentgenology Various factors of importance for the doses actually received are discussed e g voltage and filtration photographic technique properties of films fluoroscopy and intensifying screens image intensifiers TV camera tubes It is known from practical experience that only after years of efficient training under competent guidance is the radiologist able to perform examinations with minimal dosage and optimal diagnostic value so that unnecessary retakes are avoided This should be a warning to those with insufficient training not to overtax their capacity Dose measurement apparatus and radiation protection materials are also discussed under this heading

The second group of papers treats selected problems of radiobiology (the yield of free radicals by irradiation for various molecular configurations amino acid metabolism after sublethal and lethal irradiation of mice and other animals as well as in radiotherapy patients and the combined effects of irradiation and skin wounds on serum albumins and globulins) Histopathologic observations on radiation injuries in duodenal epithelium and other tissues and the effect of whole body irradiation on adrenal cortex activity are also included

The third theme is medical supervision of occupationally exposed staff The medical criteria for allowing or prohibiting a certain person to take work entailing radiation hazards are discussed in a useful way and it is pointed out that in many borderline cases permission should be given subject to certain limitations e g work with unsealed radionuclides forbidden or work permitted only with activities under a specified limit The psychical constitution of the persons examined should be better considered than is often the rule Three of the papers deal specifically with medical supervision at a university, a nuclear research centre and in the uranium industry as well as in the manufacture of fuel elements

A few papers appear under the heading for discussion They concern two different hematologic effects of radiation a case of heavy irradiation in a criticality accident and a number of cases of skin carcinoma produced by the long carrying of quacksalver radium compresses A warning is issued against such devices and similar uses of radium and radon

The book will be valuable to those with various interests in radiation protection especially diagnostic radiologists and those responsible for the medical supervision of radiologic work

Sten Benner

Table 2

Calculated doses to bone marrow of rat femora and tibiae after injection of ⁹⁰Sr—⁹⁰Y depression of cellularity and efficiency of radiation

Mean injected dose μCi/kg	Observation time weeks	Dose in mrad			Percentage mean cellular depression	Efficiency per cent depression / total rad
		First week	Remaining period	Total		
2 70	6	530	1 070	1 600	24 8	0 015
2 4	12	500	2 060	2 560	27 4	0 011
1 40	6	280	550	830	22 2	0 027
1 26	12	250	1 020	1 270	27 5	0 022
0 124	6	24	49	73	12 8	0 18
0 130	12	26	105	131	17 0	0 13
1 56 10-	6	3 5	8 1	11 6	15 9	1 4
1 42 10-	12	3 2	15 2	18 4	9 7	0 53
1 51 10	6	0 34	0 79	1 13	0 2	0 18
1 44 10-	6	0 32	0 75	1 07	—1 0	—1 0
1 44 10-	6	0 32	0 75	1 07	3 3	3 1
1 29 10	12	0 29	1 38	1 67	4 3	2 5
1 35 10-	12	0 30	1 45	1 75	6 6	3 8
0 95 10-	12	0 21	1 02	1 23	—0 1	—0 1
1 61 10-	18	0 36	2 66	3 02	2 3	0 76
1 26 10-	18	0 26	2 08	2 36	0 8	0 33
1 36 10	6	0 031	0 071	0 10	2 5	25
1 44 10-	12	0 032	0 154	0 19	—1 6	—10
1 32 10-	18	0 030	0 218	0 25	2 5	10

rat population in the animal house of the Norwegian Radium Hospital the coefficient of variation being about 10 per cent The variation between litter mates was considerably smaller however In a series of 15 pairs of litter mates the variation within sibships was a third of that between sibships

Material and Methods For the present investigation, pairs of litter mates of the same sex were used one as test animal the other as control The animals were about 2 to 3 months old when injected and weighed from 135 g to 300 g Weight difference within pairs was in general less than 20 g Radioactive strontium chloride was injected intraperitoneally in a single dose of 0 5 or 0 25 ml made up by dilution of a stock solution The control animal was given placebo injection of distilled water The test animal and its control lived under identical conditions

The animals were killed by dislocation of the neck at the end of the experi

Table 1

Cellularity and radioactivity in rat femora and tibiae after injection of ^{90}Sr

Dose injected µCi/kg	Observation time weeks	Percentage of cell content		Content of strontium 90		
		Mean	Range	Mean dpm	Range dpm	pCi/g Ca
2	6	75	69— 81			
	12	73	67— 78			
1	6	78	68— 86	29 000	26 000—33 000	37 700
	12	73	68— 79			
0 1	6	87	84— 91	4 180	3 400— 4 900	5 430
	12	83	78— 88	2 660	2 570— 2 800	3 460
0 01	6	84	81— 88	347	269— 420	450
	12	90	87— 92	289	140— 427	380
0 001	6	100	99—101	45	35— 50	59
	6	101	97—106	47	36— 66	61
	6	97	90—100	57	48— 72	74
	12	96	94— 98	30	8— 42	39
	12	93	86—101	42	34— 47	55
	12	100	99—101	29	28— 30	38
	18	98	92—107	17	5— 33	22
	18	99	96—103	52		68
0 0001	6	98	88—101	8		10
	12	102	99—105	6		8
	18	98	94—104	11		14

There were four and three rats in the 5th and 6th groups in the others five In the last four groups bones were pooled within groups and no range can be given for these Open spaces in the columns recording the ^{90}Sr content indicate that no measurement was made

decreased during the ensuing time, restoratory processes took place, leading to a certain hyperplasia of marrow cells (Vlasov 1964)

The aim of the present investigation was to determine the dose effect relationship of small amounts of ^{90}Sr in causing detectable reduction in the number of haematopoietic cells in the bone marrow of rats Reductions of the order of 10 to 15 per cent or more can be detected in histologic sections but cannot be expressed quantitatively in precise terms Counting of cells in sections is difficult to perform, and the sources of error are considerable, but by using a counting chamber a high degree of accuracy may be reached and by this method numerical reductions under 10 per cent can be detected and quantitatively determined (Stokke 1966)

The number of nucleated cells in the bone marrow will normally vary from one animal to another This variation has previously been determined in the

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1 44 10⁻	6	0 32	0 75	1 07	3 3	3 1
1.29 10⁻	1	0 29	1 38	1 67	4 3	2 5
1 35 10⁻	12	0 30	1 45	1 75	6 6	3 8
0 95 10⁻	12	0 21	1 02	1 23	—0 1	—0 1
1 61 10⁻	18	0 36	2 66	3 02	2 3	0 76
1 26 10	18	0 28	2 08	2 36	0 8	0 33
1 36 10⁻	6	0 031	0 071	0 10	2 5	25
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	12	90	87— 92	289	140— 427	380
0 001	6	100	99—101	45	35— 50	59
	6	101	97—106	47	36— 66	61
	6	97	90—100	57	48— 72	74
	12	96	94— 98	30	8— 42	39
	12	93	86—101	42	34— 47	55
	12	100	99—101	29	28— 30	38
	18	98	92—107	17	5— 33	22
	18	99	96—103	52		68
0 0001	6	98	88—101	8		10
	12	102	99—105	6		8
	18	98	94—104	11		14

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The aim of the present investigation was to determine the dose effect relationship of small amounts of ^{90}Sr in causing detectable reduction in the number of haematopoietic cells in the bone marrow of rats Reductions of the order of 10 to 15 per cent or more can be detected in histologic sections but cannot be expressed quantitatively in precise terms Counting of cells in sections is difficult to perform, and the sources of error are considerable, but by using a counting chamber a high degree of accuracy may be reached and by this method numerical reductions under 10 per cent can be detected and quantitatively determined (STOKKE 1966)

The number of nucleated cells in the bone marrow will normally vary from one animal to another This variation has previously been determined in the

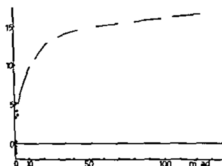


Fig 2 Percentage depression of bone marrow cellularity in relation to doses calculated to have been absorbed in marrow of femur and tibia after intraperitoneal injection of Sr the ordinate giving the mean depression of cellularity in groups of 5 test animals relative to paired s b controls and the abscissa the total dose in the experimental period ○ corresponds to 6 weeks and + to 12 weeks

values have been used in the dose calculations Since five animals at the most were used in each group no attempt has been made to calculate the error of the mean, instead the range of observed values has been indicated wherever possible The experiments were performed over a period of about two years more or less in the order of decreasing concentrations

Dose calculations The results of dose calculations are given in Table 2 Retention of the intraperitoneally injected ^{90}Sr—^{90}Y solution has been assumed to follow a pattern similar to that after injections of ^{85}Sr in mice described by NILSSON et coll (1967) and in rats described by COHN & GUSMANO (1967) These authors found by whole body counting that retention had two clearly different phases The first phase lasted for about a week, and was characterized by a rapid excretion of about 60 per cent of the amount injected The second phase consisted of a much slower rate of excretion

In the present calculations the first phase has been presumed to last for a week The rates of the two phases were determined from the skeletal content of ^{90}Sr at 6 and 12 weeks after injection (Fig 1) It was assumed that during the first week the material injected is homogeneously distributed in the whole rat and that excretion takes place at a uniform rate from all tissues The dose absorbed by the marrow of the femora and tibiae will be determined by the mean radionuclide concentration and by the geometry of the tissues surrounding these bones (PARMLEY et coll 1962 BOND & FEINENDEGEN 1966)

For the remaining part of the observation period it has been assumed that ^{90}Sr—^{90}Y is found only in the skeleton and that the excretion takes place at a lower rate (Fig 1) This rate was taken to be independent of the amount injected but in accordance with the observed levels of incorporation it was assumed that for the two larger injection amounts of the radionuclide about 40 per cent of the total is bound to the skeleton and for the three smaller in

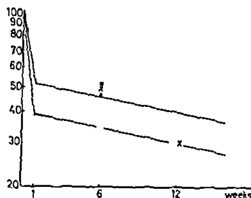


Fig. 1. Presumed retention pattern of ^{90}Sr after intraperitoneal injection expressed as percentages of amount injected (ordinate), the points representing the ^{90}Sr body burden calculated from amounts measured in *femora and tibiae at times* given (abscissa). Semilog scale. ● 1.5 μCi per kg bodyweight, + 0.15 μCi, × 0.015 μCi and ○ 0.0015 μCi (approximate concentrations). It should be observed that the two symbols + and × are meant to coincide at 12 weeks and should have been superimposed but have for the sake of clarity *been given separately*.

mental period. The marrow in the shafts of both femora and tibiae were taken out in separate aliquots, weighed, suspended in 3 per cent acetic acid, and transferred to a Burkers counting chamber for counting (STOKKE 1966). The counts were recorded as the number of cells per milligram of marrow, and the mean of these four counts from the test animal was expressed as a percentage of the corresponding value from the control. Experiments were usually performed with *five pairs of animals for each dose*.

The length of the experimental period and the magnitude of the dose were determined in preliminary experiments. The minimum useful time of observation was found to be 6 weeks with the small doses used, after this time conditions became fairly stabilized.

The bone marrow of the femora and tibia was removed, and the ^{90}Sr content of the bony parts determined. This was done by radiochemical isolation of strontium, followed by standard and low level proportional β counting. The results have been expressed as *disintegrations per minute per gram of* bone ash. The determination of radioactivity in the bone ash was carried out separately for each test animal, and the group mean value calculated. Excepted were the groups injected with the smallest amounts of ^{90}Sr, in which the skeletal parts from the five test animals of the group were pooled in one analysis. The background was determined by pooling *all skeletal material of the control animals* of the group. This value has been subtracted from the mean and range values of the corresponding test group. The results are presented in Table I as pCi ^{90}Sr/g Ca on the basis of 35 per cent Ca in the bone ash.

Observations. The observations are summarized in Table 1. It will be noted that the amount injected was constant within each group, and the concentration will therefore vary inversely with the weight of the rat. The values in the first column therefore give only the order of magnitude of concentration. Exact

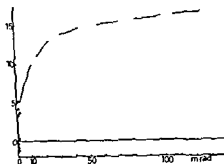


Fig 2 Percentage depression of bone marrow cellularity in relation to doses calculated to have been absorbed in marrow of femur and tibia after intraperitoneal injection of Sr the ordinate giving the mean depression of cellularity in groups of 5 test animals relative to paired sib controls and the abscissa the total dose in the experimental period ○ corresponds to 6 weeks and + to 12 weeks

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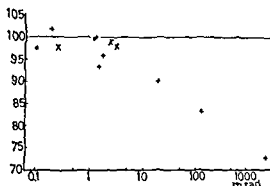


Fig 3 Percentage cellularity of bone marrow in relation to doses calculated to have been absorbed in bone marrow of femur and tibia after intraperitoneal injection of ^{90}Sr The ordinate giving the mean cellularity in groups of 5 test animals relative to paired sib control and the abscissa the total dose in the experimental period Semilog scale ○ corresponds to 6 weeks + to 12 weeks and × to 18 weeks

jection amounts about 50 per cent The doses absorbed by the bone marrow have been calculated on these assumptions and on the basis of the theoretical and calculated absorbtion constants of PARMLEY et coll (loc cit) The doses calculated for the two excretion phases, as well as the efficiency of radiation calculated in terms of percentage cellular depression in the bone marrow per rad total dose, are given in Table 2

In Fig 2, the cellularity of the bone marrow has been plotted against the total doses calculated in the lower range It will be seen that the relationship between calculated doses and the depression of cellularity is not easily interpreted It appears that doses in the ten millirad range lead to a depression by some 10 to 15 per cent, and that even a few millirad may have some effect A biphasic reaction pattern in relation to the dose appears possible

It appeared by plotting the data on a semilog scale as shown in Fig 3 that the effect beyond the dose range of a few millirad may be described by a power law, *the effect being proportional to the logarithm of the dose* For the two lower groups of doses the data do not conform to this description

Finally, it was revealed by plotting *the efficiency of the radiation on a log log* scale as in Fig 4 that the radiation efficiency at all dose levels appears to be limited by the line log efficiency = — const log dose

However in the lowest dose range, where both positive and negative values are observed, *the validity of this hyperbolic function is quite uncertain*

The present material is not large enough to determine how the cellularity varies with time within any of the dose groups In the range of *1 to 3 mrad* where there are several observations at the 6 , 12 and 18 week periods, it could be surmised that a steady state situation might be present However, the effects are not unambiguous, and no definite conclusion can be drawn

The present material permits no differentiation between the effects of the

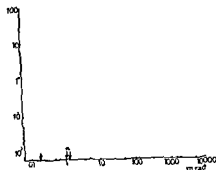


Fig 4 Efficiency of radiation (i e percentage depression of bone marrow cellularity per rad) in relation to doses calculated to have been absorbed in bone marrow of femur and tibia after intraperitoneal injection of Sr the ordinate giving the depression per rad total dose over the experimental period and the abscissa the total dose in the experimental period Log log scale The arrows indicate three cases of negative depression ○ corresponds to 6 weeks + to 12 weeks and × to 18 weeks

relatively high dose of the first week and those of the lower but approximately constant dose rate of the subsequent period This is because a high or low dose during the first week is invariably associated with a similarly high or low dose during the remaining observation period According to NILSSON (1967) the latter phase is more important for tumor induction in mice If the cellular depression observed is in fact the reflection of a steady state situation (LAMERTON 1961, 1968), one would likewise expect the long term dose rate to be o decisive importance since recovery from the dose of the first week should be completed long before the first observation at 6 weeks

Discussion

Whatever the biologic significance of the reduction of bone marrow cellularity it is interesting that it appears possible to demonstrate a biologic effect in mammals at a dose level of a few millirad per week Biologic effects in the millirad range have so far been observed only in experiments on fungal growth rate (FORSBERG 1943)

The present dose calculations are not extreme in one direction or another Due to the quantitative limits determined by the amount of radioactivity injected and by the concentration measured in the skeleton the leeway afforded for more extreme values is not great The dose of the rapid excretion phase would certainly be higher if this phase were to last longer than observed in the mouse However if it were to last for two weeks instead of one the dose contribution of this phase would increase by at most one third of that calculated at present It appears possible on the basis of the data of COHN & GUSMANO (1967) obtained with considerably higher amounts of radioactivity that this phase is in fact shorter Furthermore, it could be that the dose accumulated during the

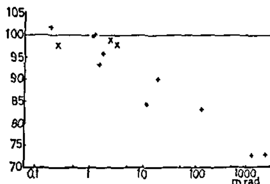


Fig 3 Percentage cellularity of bone marrow in relation to doses calculated to have been absorbed in bone marrow of femur and tibia after intraperitoneal injection of ⁹⁰Sr the ordinate giving the mean cellularity in groups of 5 test animals relative to paired sib control and the abscissa the total dose in the experimental period Semilog scale ○ corresponds to 6 weeks + to 12 weeks and × to 18 weeks

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It appeared by plotting the data on a semilog scale as shown in Fig 3 that the effect beyond the dose range of a few millirad may be described by a power law, the effect being proportional to the logarithm of the dose For the two lower groups of doses, the data do not conform to this description

Finally, it was revealed by plotting the efficiency of the radiation on a log log scale as in Fig 4 that the radiation efficiency at all dose levels appears to be limited by the line log efficiency = — const log dose

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The present material is not large enough to determine how the cellularity varies with time within any of the dose groups In the range of 1 to 3 mrad where there are several observations at the 6 , 12 and 18 week periods, it could be surmised that a steady state situation might be present However, the effects are not unambiguous, and no definite conclusion can be drawn

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slow excretion phase may be considerably lower, if data for the male mouse apply to rats of both sexes It has been shown by MULLER (1967) that the ^{90}Y daughter is rapidly transferred from the skeletally deposited ^{90}Sr to the testes This leads on the one hand to an unexpected genetic dose contribution from ^{90}Sr—^{90}Y (LUNING et coll 1963) and on the other hand to a concomitant reduction of the bone marrow dose by about 70 per cent in the rat This aspect is not revealed by whole body counting (COHN et coll 1967, NILSSON et coll 1967) or by the present radiochemical measurements, due to the reestablishment of the ^{90}Sr—^{90}Y equilibrium post mortem

SUMMARY

Bone marrow cellularity in the rat has been measured after injection of small amounts of ^{90}Sr Reduced cellularity could be observed 6 and 12 weeks after injection of 1 5 $\times$ 10 ^{3} μCi/kg leading to accumulated doses of 10 to 20 millirad

ZUSAMMENFASSUNG

Die Zellenzahl des Knochenmarkes wurde nach Injektion kleiner Mengen von Strontium 90 in Ratten gemessen Eine Reduktion der Zellenzahl wurde 6 und 12 Wochen nach der Injektion von 1,5 $\times$ 10 ^{3} μCi/kg festgestellt was einer akkumulierten Dosis von 10 bis 20 millirad entspricht

RÉSUMÉ

Les auteurs ont fait des numerations des cellules de la moelle osseuse sur le rat après injection de petites quantites de ^{90}Sr Ils ont observé une diminution du nombre des cellules six et douze semaines après l injection de 1 5 $\times$ 10 ^{3} μCi/kg de ^{90}Sr donnant une dose cumulative de 10 à 20 millirad

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Table 1

Retention of ^{85}Sr in mothers — Figures give activity in per cent of initial measurement mean + SE (correction for decay)

Tim between i ject on and measurement	Days before tart of lactation				Unmated control
	41	23	23	1	
1 week	36 6±1 47	36 7±0 96	33 6±1 00	26 0±1 10	37 7±2 24
1 month	24 7±0 86	19 2±0 70	17 7±0 60	14 6±0 96	26 6±0 53
2 month	12 5±0 78	10 2±0 65	9 4±0 37	10 2±0 52	18 2±0 39
3 m nths	10 3±0 74	7 6±0 42	7 4±0 18	7 9±0 47	18 5±0 50

* Males removed at times of b rth

of about 70 × 10 cpm measured in the Small Animal Counter used in the experiment and described in an earlier paper (NELSON et coll 1965)

The interval between administration of radiostrontium and start of lactation in the different groups is shown in the schedule below which also gives the times when the animals were measured after the strontium administration

There were 20 mice in each group

Injection time (before start of lactation)	*Interval between injection and measurement*
41 days 23 days 23 days (males removed at times of birth) 1 day Unmated control	Zero time 1 week 1 month, 2 months and 3 months

In all groups but the control the females were mated to untreated CBA males with one female and one male in each cage The males remained in the cages throughout the experiment except in the second of the 23 day groups Here the male was removed 2 or 3 days before birth of the litter and was replaced about 10 days later This was done in order to decrease the force of the breeding rate in this group The females in the unmated control group were caged five together

The measurements in the female mice are given as per cent of the initial value calculated for every individual Correction has been made for decay by time The results are given in Table 1 and Fig 1

FROM THE DIVISION OF RADIOBIOLOGY (DIRECTOR DOCENT A NELSON), RESEARCH INSTITUTE OF NATIONAL DEFENCE, SUNDBYBERG, SWEDEN

INFLUENCE OF LACTATION ON RETENTION OF RADIOSTRONTIUM IN MICE

by

C RONNBACK, A NELSON and A NILSSON

The influence of gestation and lactation on the induction of tumours by ^{90}Sr in mice was investigated by NILSSON (1967) He found that the latency period was extended and the bone tumour rate decreased in a mated group giving suck in comparison with an unmated group These results initiated an investigation of the excretion rate of ^{85}Sr in groups of unmated mice, mated mice, and mated mice giving suck (NILSSON et coll 1967) The influence of gestation alone was negligible Lactation, however, significantly decreased the retention Since in their investigation the female mice were injected on different days of pregnancy only, supplementary data regarding the effect of lactation on retention when strontium was administered at different times before mating seemed desirable In addition, further information on the amount of strontium transferred to the young via the milk should be obtainable

Material and Methods Female CBA mice, aged about 70 days were injected with 0 3 ml of a solution of ^{85}Sr in saline amounting to about 0 3 μCi per animal The activity thus administered to the animals gave an initial value

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Table 1

Retention of ^{85}Sr in mothers — Figures give activity in per cent of initial measurement mean ± SE (correction for decay)

Time between injection and measurement	Days before start of lactation				Unmated control
	41	23	23*	1	
1 week	36 6±1 47	36 7±0 96	33 6±1 00	26 0±1 10	37 7±[illegible] 24
1 month	24 7±0 8[illegible]	19 2±0 70	17 7±0 60	14 6±0 96	26 6±0 53
2 months	12 5±0 78	10 2±0 6[illegible]	9 4±0 37	10 2±0.5[illegible]	18 2±0 39
3 months	10 3±0 [illegible]4	7 6±0 4[illegible]	7 4±0 18	7 9±0 47	18 5±0.50

* Males removed at times of birth

of about 70 × 10³ cpm measured in the Small Animal Counter used in the experiment and described in an earlier paper (NELSON et coll 1965)

The interval between administration of radiostrontium and start of lactation in the different groups is shown in the schedule below which also gives the times when the animals were measured after the strontium administration

There were 20 mice in each group

Injection time (before start of lactation)	*Interval between injection and measurement*
41 days 23 days 23 days (males removed at times of birth) 1 day Unmated control	Zero time 1 week 1 month 2 months and 3 months

In all groups but the control the females were mated to untreated CBA males with one female and one male in each cage The males remained in the cages throughout the experiment except in the second of the 23 day groups Here the male was removed 2 or 3 days before birth of the litter and was replaced about 10 days later This was done in order to decrease the force of the breeding rate in this group The females in the unmated control group were caged five together

The measurements in the female mice are given as per cent of the initial value calculated for every individual Correction has been made for decay by time The results are given in Table 1 and Fig 1

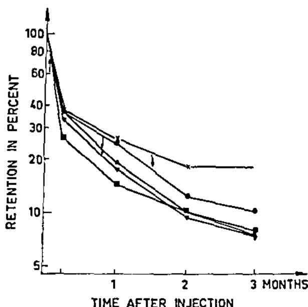


Fig 1 Results of measurement of retention of ^{85}Sr in mice at different intervals before start of lactation ● 41 days ▲ 23 days ▼ 23 days (males removed at time of birth) ■ 1 day × unmated control

In addition to these measurements the activity in the young was measured at 1, 2 and 3 weeks after birth The first and the second litters, and in group 4 also the third litter, were measured The results are given as counts per minute and are shown in Table 2 and Fig 2

Results

The rate of excretion of ^{85}Sr from the female mice is shown in Table 1 and Fig 1

The unmated control females showed the highest retention, followed by the females which were injected 41 days before the start of lactation As may be seen in Fig 1, the excretion rate in the later group was enhanced at the start of lactation, the time of which is indicated by the arrow

The females injected with strontium 23 days before start of lactation (i e 2 days before mating) show during the first month a higher excretion rate than those injected 18 days earlier After the lactation had started, the excretion rate seemed to be of the same order of magnitude in these two experimental groups As was described earlier, there also was one group of females, injected 23 days before the start of lactation, with a lower breeding rate The retention in this group was somewhat lower than in the first mentioned 23 day group, though not statistically different

The highest excretion rate occurred in females injected 1 day before start of lactation Also in this group a very high excretion was noted after start

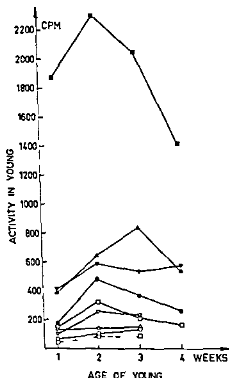


Fig 2 Results of measurement of the activity in the young mice at different interval before start of lactation ● 41 days ▲ 23 days ▼ 23 days (males removed at time of birth) ■ 1 day The black symbols indicate the first litter open symbol the second litter and the dotted line the third litter

of lactation in this case already during the first week After one month the rate decreased and 3 months after injection the retention was practically the same as for the 23 day groups

The strontium content in the young reflected the retention in their mothers the content increasing with decreasing time between injection and start of lactation (see Fig 2 and Table 2)

There was in general however a great difference between the strontium content in the litters from females injected 1 day before start of lactation compared to those from females injected earlier during (or before) pregnancy The retention in the young reached its highest point at the age of 2 weeks (in one group at 3 weeks) After that time suckling decreased and thus the strontium uptake via the milk the retention curve shows a negative slope After the 3 week measurement the young were weaned and given ordinary food At this time a new litter usually was born in the first mentioned 23 day groups and within 24 hours the females were again made pregnant In the

Table 2

Activity in young from mothers which had been injected with ^{85}Sr at different times before start of lactation — Measurements corrected for decay and given as counts per minute in thousands

Time for injection of mother	Age of young at time of measurement	Number of litters measured	Activity	
			In young ($\bar{x} \pm$ S.E.)	In mothers ($\bar{x} \pm$ S.E.)
41 days before lactation	*1st litter*			
	1 week	12	0.17 ± 0.03	10.7 ± 0.6
	2 weeks	11	0.48 ± 0.03	7.6 ± 0.7
	3 weeks	12	0.36 ± 0.03	7.4 ± 0.4
	4 weeks	11	0.26 ± 0.02	6.7 ± 1.1
	2nd litter			
	1 week	9	0.06 ± 0.01	6.7 ± 1.1
	2 weeks	8	0.10 ± 0.01	7.1 ± 0.7
	3 weeks	6	0.13 ± 0.04	6.1 ± 0.6
23 days before lactation	*1st litter*			
	1 week	17	0.39 ± 0.05	13.3 ± 0.5
	2 weeks	17	0.63 ± 0.03	10.4 ± 0.4
	3 weeks	17	0.84 ± 0.04	8.8 ± 0.3
	4 weeks	16	0.53 ± 0.04	7.4 ± 0.3
	2nd litter			
	1 week	13	0.13 ± 0.03	7.1 ± 0.3
	2 weeks	13	0.14 ± 0.02	6.7 ± 0.4
	3 weeks	12	0.15 ± 0.04	6.4 ± 0.6
23 days before lactation. Males removed at times of birth	*1st litter*			
	1 week	15	0.40 ± 0.05	12.5 ± 0.3
	2 weeks	15	0.59 ± 0.04	9.4 ± 0.2
	3 weeks	15	0.53 ± 0.04	8.3 ± 0.4
	4 weeks	15	0.57 ± 0.03	—
	2nd litter			
	1 week	5	0.10 ± 0.04	—
	2 weeks	4	0.27 ± 0.02	6.9
	3 weeks	2	0.23 ± 0.12	3.6
1 day before lactation	*1st litter*			
	1 week	17	1.87 ± 0.08	16.5 ± 0.7
	2 weeks	17	2.25 ± 0.10	12.9 ± 1.0
	3 weeks	17	2.03 ± 0.14	10.5 ± 0.4
	4 weeks	17	1.40 ± 0.06	9.0 ± 0.5
	2nd litter			
	1 week	14	0.15 ± 0.03	9.0 ± 0.5
	2 weeks	14	0.32 ± 0.03	8.2 ± 0.6
	3 weeks	14	0.21 ± 0.02	7.7 ± 0.6
	4 weeks	13	0.16 ± 0.02	6.0 ± 0.3
	3rd litter			
	1 week	12	0.04 ± 0.01	6.8 ± 0.4
	2 weeks	10	0.09 ± 0.03	6.3 ± 0.4
	3 weeks	11	0.09 ± 0.02	6.5 ± 0.4

other 23 day group the females were not pregnant during the suckling period the mating occurring after the litter was weaned

Measurements in the second litter produced a similar picture with a lower strontium content than in the first litter The differences between the groups also diminished

The results of measurements in the young and corresponding values from the mothers measured on the same occasion, are presented in Table 2 It should be observed that the measurements in the first litter at the age of 4 weeks was made at the same time as the first week measurement in the second litter

Comments It is apparent from our previous investigation (NILSSON et coll 1967) that in mice the gestation does not significantly enhance the excretion of radiostrontium administered before mating KOLLMER & KRIEGEL (1965 a) found in rats however that the 48 hour retention of ^{90}Sr administered at the end of gestation was significantly lower than the 48-hour retention in virginal rats Our present investigation, in which ^{85}Sr was administered 41 days and 23 days before partus confirmed that gestation does not influence the rate of excretion

Lactation on the other hand was the important factor regarding enhancement of excretion of radiostrontium even when it was administered 41 days before lactation

The stimulating effect of lactation on the metabolically active areas of the bone tissue primarily the epiphyse metaphyse regions seems to have caused this increased excretion as has also been shown by KOLLMER & KRIEGEL (1965 b)

As expected the uptake of strontium in the litters is dependent on the elapse of time between administration and partus Due to the accumulation of strontium during the first week of lactation the greatest retention is measured at 2 weeks After this time the suckling intensity decreases leading to a decrease of retention

The fact that strontium such a long time after the administration can be mobilized from the bone tissue by a normal metabolic process constitutes a stimulation to further investigation of the underlying fundamental processes

SUMMARY

The influence on the excretion rate of the interval between administration of radiostrontium and start of lactation was studied in CBA mice The radionuclide ^{85}Sr was administered 41 23 and 1 day respectively before start of lactation and the retention was studied during 3 months The excretion rate decreased with increasing interval between administration and lactation Even the group receiving radiostrontium 41 days prior to lactation displayed enhancement of the excret on rate during lactation

ZUSAMMENFASSUNG

Der Einfluss des Zeitintervalles zwischen der Verabreichung von Radiostrontium und dem Beginn der Laktation auf die Ausscheidungsgeschwindigkeit wurde bei CBA Mausen studiert Das Radionuklid ^{85}Sr wurde bzw 41 23 und 1 Tag bevor dem Beginn der Laktation verabreicht und die Rentention wurde wahrend 3 Monaten observiert Die Ausscheidung nahm mit zunehmendem Zeitintervall zwischen Verabreichung und Laktation ab Auch die Gruppe die Radiostrontium 41 Tage bevor der Laktation erhielt wies eine Zunahme der Ausscheidungsrate wahrend der Laktation auf

RÉSUMÉ

Les auteurs ont étudié l influence sur la vitesse d excrétion de l intervalle entre l administration du strontium radioactif et le début de la lactation sur des souris CBA Le radionuclide ^{85}Sr a été administré respectivement 41 23 et 1 jour avant le début de la lactation et sa rétention a été étudié pendant trois mois La vitesse d excrétion diminue à mesure qu augmente l intervalle entre l administration du radionuclide et la lactation Mais le groupe qui a reçu le strontium radioactif 41 jours avant la lactation a présenté une accélération de l excrétion pendant la lactation

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RADIATION INDUCED INVOLUTION OF THE LYMPHATIC ORGANS OF THE YOUNG CHICKEN

by

JAMES L MONTOUR

Thymic weight loss and splenic weight loss following whole body irradiation have been shown to be sensitive indicators of radiation damage (CARTER *et coll* 1950) The dose dependence of these responses has made them a valuable measure of the relative biologic effectiveness (RBE) of mixed radiations or of radiations of unknown quality (CARTER et coll 1950 HARRIS et coll 1952 HARRIS et coll 1953) The thymus and the spleen are similarly radiosensitive in various mammals despite widespread differences in the radiosensitivity of the *species* as measured by the 30-day lethality (BLOOM 1954)

Three major lymphatic organs are found in the chicken the thymus the bursa of Fabricius and the spleen The thymus and the spleen are analogous to the mammalian thymus and spleen but the bursa is apparently a uniquely avian organ JOLLY (1913) reported involution of both the thymus and the bursa following whole body roentgen irradiation and JACQUEZ & KARNOFSKY (1950) and ATKINSON et coll (1961) described histologic changes in the lympho

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epithelial organs of the chicken similar to those observed following whole body irradiation of the mouse. *None of the studies reported to date, however, have* quantitatively examined the acute involution of the lymphatic organs of the chicken following graded doses of radiation.

This study was designed to examine both the radiation dose sensitivity of the chicken's lymphatic tissues and the time pattern of involution following single exposures to roentgen radiation. Since early radiation mortality in the young chicken is acutely sensitive to dose rate, or total exposure time (STEARNER et coll. 1957), the dose rate sensitivity of the chicken's lymphatic tissues was also examined. Comparable radiation exposures were performed at both a low rate (8.8 R/min) and a high dose rate (96.5 R/min).

Materials and Methods

Exposure conditions. The source of radiation was a conventional therapy machine operated at 250 kVp and 15 mA with 0.5 mm Al and 1.0 mm Cu added filtration. The first half value layer, as measured 55 cm from the target, was 1.6 mm of Cu. Exposures measured with a commercially calibrated Victoreen Condenser R-Meter were *0 R, 50 R, 100 R, 200 R*, and *400 R*.

High dose rate (HDR). Groups of 16 chicks were exposed in a cylindrical polyethylene chamber 24.75 cm (9 3/4 inches) in diameter and 4.45 cm (1 3/4 *inches) in height, which was rotated in the radiation field at approximately* 2/3 RPM. At a distance of 55 cm from the radiation source, the dose rate measured under the conditions of maximum backscatter at the midpoint of the exposure chamber was 96.5 R/min. A decrease in dose of less than 5 % was observed at the perimeter of the exposure field.

Low dose rate (LDR). Groups of 20 chicks were exposed in a cylindrical cardboard chamber 32 cm (12.5 inches) in diameter and 7.6 cm (3.0 inches) in height, which was rotated at approximately 2/3 RPM. At a distance of 185.4 cm from the target, the dose rate measured under conditions of maximum backscatter was approximately 8.8 R/min. A difference of less than 1 % was found between the doses measured at the midpoint and at the *periphery of the* exposure chamber.

Animals. Single comb white leghorn cockerels obtained from Klager Hatchery Saline, Michigan, shortly after hatching were housed 50 per shelf in a standard chick brooder. Purina starter mash and water were available ad libitum. Radiation exposures were performed on the tenth day of age. Because the

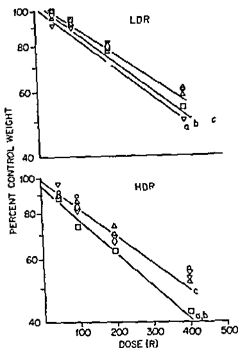


Fig 1 Lymphatic tissue dose response to low dose rate and high dose rate roentgen irradiation Total lymphatic tissue following exposure to 0 R 50 R 100 R 200 R or 400 R at either 8 8 R/min (LDR) or 96 5 R/min (HDR) At each dose the total lymphatic tissue is plotted for the 5 days following exposure ○ day 1 □ day 2 △ day 3 ▽ day 4 ◇ day 5 Three lines have been drawn through the sets of points at each dose the points of maximum depression at each dose (a) the points of maximum 1—2 day depression (b) and the average of all points at each dose (c) In the case of the high dose rate (HDR) exposures the first two lines (a b) are the same

lymphatic tissues of the chick like those of mammals are sensitive to adrenal corticoid release following stress (GARREN et coll 1956, NEWCOMER et coll 1966) three control groups were maintained Two groups were handled as high dose rate and low dose rate animals, respectively, and the third group was maintained as an unstressed cage control The lymphatic organ weights of both stressed control groups were reduced by approximately 5 % as compared to those of the cage controls All animals including the experimental control series were retained in their exposure chambers for a period of time equal to that of the longest exposure

Dissection For 5 days following exposure a minimum of 8 chicks per exposure group were killed daily and the thymus bursa and spleen removed from each The organs were immediately cleaned of extraneous tissues and their wet weights determined to the nearest 0 1 mg Because a direct relationship exists between lymphatic organ weight and body weight in the young chicken, absolute organ weights were converted to mg/100 g body weight Since even the young chicken is capable of retaining several grams of food in its crop, the

Table 1

Response of chick lymphatic tissue to HDR and LDR roentgen exposures — Values derived from Fig 1

	ED_{50}		Slope		y intercept		Slope LDR
	LDR	HDR	LDR	HDR	LDR	HDR	Slope HDR
All points	475 R	395 R	0 113	0 125	106 %	98 %	0 85
Max involution (1—2 d)	410 R	305 R	0 128	0 140	105 %	95 %	0 91
Max involution (1—3 d)	400 R	305 R	0 128	0 140	102 %	95 %	0 91

Comparison of the slopes of the dose response lines indicates that exposure at a low dose rate (LDR) was only 85 % to 91 % as effective per roentgen in producing lymphatic involution as exposure at a high dose rate (HDR) In addition the y intercepts of the HDR lines were below those of the comparable LDR lines

Table 2

Total lymphatic tissue weight following irradiation

Dose	Dose rate	Total lymphatic tissue weight (mg/100 g bw)				
		Day 1	Day 2	Day 3	Day 4	Day 5
0 R		858 (83)	935 (89)	988 (102)	1049 (107)	1084 (117)
50 R	LDR	849 (84)	926 (88)	948 (94)	955 (112)	1062 (122)
	HDR	781 (83)	823 (92)	899 (104)	1018 (111)	965 (117)
100 R	LDR	781 (83)	888 (89)	929 (94)	944 (109)	1019 (114)
	HDR	764 (85)	692 (85)	850 (91)	850 (109)	900 (114)
200 R	LDR	609 (78)	734 (83)	771 (94)	850 (103)	856 (107)
	HDR	601 (83)	589 (89)	721 (98)	713 (104)	726 (120)
400 R	LDR	515 (80)	505 (85)	573 (91)	514 (97)	650 (106)
	HDR	476 (81)	402 (84)	514 (91)	556 (97)	607 (108)

Control values (OR) are the averages of 16 measurements each all other values are averages from 8 measurements each average body weight in grams is shown in parentheses

animals to be dissected each day were removed from the brooder before feeding began in the morning Any food found in the crop was removed before body weight measurements were taken

Results

The dose response of the chick lymphatic tissues to irradiation is presented in Fig 1 Each point represents the average total lymphatic tissue weight of eight birds expressed in percentage of the value of the stressed control

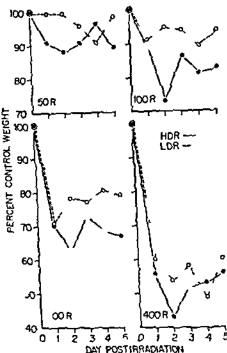


Fig. 2 Daily pattern of involution following roentgen irradiation Exposures to 50 R 100 R 200 R or 400 R at 8 8 R/min (broken lines) were less effective in producing lymphatic tissue involution than were comparable exposures at 96 5 R/min (solid lines)

groups Three lines have been drawn through the two sets of points (a) through the points of maximum depression at each dose (b) through the points of maximum 1—2 day depression, and (c) through the average of all points In the case of the high dose rate exposures the lines (a) and (b) are the same The organ weights following both high dose rate and low dose rate exposures are well described by either a linear or a log linear relationship with linear dose The latter representation was chosen since it is typical of the response of cell populations to increasing radiation doses

The negative slopes y intercepts and ED_{50} values obtained from the lines in Fig 1 are given in Table 1 The differences in slopes indicate that exposure at the low dose rate was 0 85 to 0 91 as effective per R as exposure at the high dose rate in producing lymphatic involution The ED_{50} values obtained either directly or by extrapolation of the lines in Fig 1 varied from 305 R (maximum involution) to 395 R (all points) for the high dose rate exposures and from 400 R (maximum involution) to 475 R (all points) for the low dose rate exposures The y intercepts of the HDR lines were 7 % to 10 % below the comparable LDR lines

The changes in organ weights as a function of time after exposure (in days) are given in Table 2 and Fig 2 for each of the four exposures Except at 50 R, where no decrease was seen following LDR exposure until the third or fourth day after exposure, the weight loss was similar for both exposure conditions on the first day after exposure, on the second day an additional decrease was seen in the weights of the lymphatic tissues in the high dose rate groups, while little or no further decrease was seen in the low dose rate groups

Discussion

Dose response The rate of acute involution of the chick lymphoepithelial organs (Fig 2) was similar to that reported for mammals after a single acute exposure to irradiation (KALLMAN et coll 1955) Maximum initial depression was reached by the first or second day after exposure and was followed by varying degrees of recovery or additional secondary injury Measured at the time of maximum depression, the ED_{50} values were 305 R (HDR) and 400 R (LDR) These doses were three to four times greater than those reported to produce 50 % involution of the mouse thymus and spleen measured at maximum depression On the fifth day after exposure, when recovery is apparent in both the mouse and the chick, the ED_{50} values are increased to 150—210 R in the mouse and to 395 R (HDR) and 475 (LDR) in the chick, the values in the latter species are still a factor of more than two higher than those in the former

The following points should be considered with respect to the use of acute involution of chick lymphoepithelial organs for the bio assay of mixed or unknown radiations

1 A linear dose versus log organ weight response is available on the first to second post irradiation day Unpublished observations indicate that this relationship is maintained at least through 600 R of whole body irradiation

2 Should different exposure groups be subjected to different degrees of stress, newly hatched chicks may be used for the assay In these animals the pituitary adrenal axis is incompletely developed, and external stress has a minimal effect on lymphatic organ weight

3 Above 650 R of acute (dose rate greater than 10 R/min) whole body irradiation, chicks begin to die in the early period (within 18 hours post exposure), complicating measurements at and above this dose

4 Although the dose sensitivity is not as great in the chick as in the mouse, the larger amount of lymphatic tissue in the chick and the greater amount of tissue remaining, particularly after doses of 400 to 600 R, make possible accurate dose estimates even with small numbers of animals

Dose rate response Measured at the ED ₀ values the low dose rate exposures were 0 74 (maximum involution) to 0 83 (average of all points) as effective as high dose rate exposures in producing lymphatic tissue involution A portion of the difference observed by this measure was the result of the difference in the y intercepts of the lines obtained from the two exposure conditions As measured by differences in the slopes of the lines in Fig 1, low dose rate exposure was still 15 % to 10 % less effective per roentgen than high dose rate exposure in producing acute involution of the chick lymphatic tissues This difference was primarily the result of additional involution in the high dose rate animals on the second day after exposure following the nearly equal involution in the two groups observed on the first day after exposure This difference was generally maintained thereafter throughout the 5 day experimental period

The observed dose rate effect can be explained by one or both of the following possibilities First the direct killing of the radiosensitive lymphocytes in the thymus bursa and spleen is a dose rate dependent event Second the high dose rate exposures initiate events outside the lymphatic tissues which by indirect or abscopal, processes cause killing of lymphocytes in these organs in addition to the direct damage from either high or lower dose rate exposures

Neither of these possibilities is excluded by the data presented in this experiment Although no evidence has been reported concerning a dose rate effect on lymphatic organ weights dose rate effects have been reported for a variety of endpoints in mammals (BATEMAN et coll 1962 CURTIS et coll 1964, RUSSELL 1965) In no case however is the dose rate effect as great as that reported here for comparable dose rates On the other hand in addition to the striking dose rate effect previously mentioned for early (48 hour) mortality in the chicken (JACQUEZ et coll 1950) a dose rate effect on 3 to 30 day mortality has also been reported which is comparable in magnitude to that reported here (TYLER et coll 1962) The early appearance of the effect only two days after exposure is consistent with a dose rate sensitivity of the radio sensitive lymphocytes themselves

Partial body exposures (MONTOUR 1967) have revealed an early (2 day) abscopal effect on the chick lymphatic organs which appears to be related to the highly dose rate dependent 48 hour mortality Exposures performed at 40 R/min have produced results similar to those reported here for exposure at 100 R/min It would seem quite possible then that even at sublethal doses damage of the type responsible for dose rate dependent mortality in the chick is being accumulated and that this damage indirectly contributes to the lymphatic involution following high dose rate exposures

The changes in organ weights as a function of time after exposure (in days) are given in Table 2 and Fig 2 for each of the four exposures Except at 50 R, where no decrease was seen following LDR exposure until the third or fourth day after exposure, the weight loss was similar for both exposure conditions on the first day after exposure, on the second day an additional decrease was seen in the weights of the lymphatic tissues in the high dose rate groups, while little or no further decrease was seen in the low dose rate groups

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SUMMARY

Ten day old leghorn cockerels were exposed to 50 R 100 R 200 R or 400 R of roentgen rays at either 8 8 R/min or 96 5 R/min Determinations of the combined weights of the thymus bursa of Fabricius and spleen were made for the ensuing 5 days Maximum depression of the weights of these organs were obtained 1 day after the low dose rate exposures and 2 days after the high dose rate exposures Measured 5 days after exposure the combined lymphatic organ weights were reduced 50 % by 395 R *when the dose rate was 96 5 R/min*

ZUSAMMENFASSUNG

Rontgenbestrahlung von 10 Tage alten weissen Leghorn Hahnen wurde bei 50 R 100 R, 200 R oder 400 R vorgenommen, entweder mit 8,8 R/min oder 96 5 R/min Gesamtgewicht bestimmung von Thymus Bursa Fabricius und Milz wurde wahrend den folgenden funf Tagen unternommen Die maximale Herabsetzung des Gewichtes dieser Organe wurde bei der niedrigen Dosisbestrahlung nach einem Tag und bei der hohen Dosisbestrahlung nach zwei Tagen beobachtet Am funften Tag nach der Bestrahlung mit 395 R war das Gewicht der lymphatischen Organe um 50 % vermindert, wenn die Dosisrate 96 5 R/min war

RÉSUMÉ

De jeunes coqs leghorn blancs âgés de 10 jours ont été exposés à des doses de 50 100 200 ou 400 R de rayons roentgen à des débits de 8 8 R/minute ou de 96 5 R/minute Le poids total du thymus de la bourse de Fabricius et de la rate a été déterminé pendant les 5 jours suivant l irradiation Le poids de ces organes atteint un minimum un jour après les irradiations à fort débit Le poids total des organes lymphatiques mesuré 5 jours après l exposition aux radiations est réduit de 50 % par une dose de 395 R quand le débit de dose est de 96 5 R/minute

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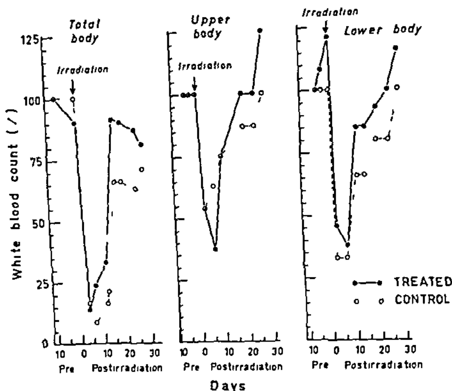


Fig 1 Effect of testosterone treatment on total upper and lower body irradiated rats

Material and Methods Male rats of the Hebrew University strain ranging in weight from 200 to 250 g were fed water and food pellets ad libitum Hypophysectomy was carried out by the parapharyngeal approach Total body exposures of 300 and 500 R and localized doses of 500 and 1 000 R were given at a dose rate of 130 R/min at 200 kV (15 mA) with filters of 0 5 mm Cu and 1 0 mm Al Animals exposed to localized irradiation were anesthetized with intraperitoneal sodium pentobarbiton (30 mg/kg) Blood samples for the leucocyte count were obtained from the tail The results were expressed as the average of all determinations for a group of rats treated alike The initial value was called 100 % Testosterone propionate was administered to one group in daily subcutaneous doses of 5 mg and to another group in daily doses of 0 5 mg per rat from a week before irradiation and during the whole experiment Five different sets of experiments were performed

In the first experiment 50 rats received total body irradiation 25 of them

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EFFECT OF TESTOSTERONE TREATMENT AND HYPOPHYSECTOMY ON THE LEUCOCYTE COUNT IN IRRADIATED RATS

by

E. ROBINSON and I. CHOWERS

The androgenic hormone, testosterone, when used in large doses stimulates erythropoiesis, primarily by a direct effect on early cell precursors (KENNEDY et coll. 1957, MIRAND et coll. 1965, SHAHIDI et coll. 1961). The possibility that this hormone may increase white blood cell production has been suggested (KENNEDY 1962, KENNEDY *et coll.* 1956) and later confirmed by BRODSKY et coll. (1964). These investigators reported that pretreatment of three cases of carcinoma with testosterone prevented significant granulocytopenia after the administration of cytotoxic agents.

In order to elucidate the mechanism of the action of testosterone, total and partial body *irradiated rats were treated with this hormone* and the leucocyte counts compared with those of irradiated but otherwise untreated rats.

The purpose of the present study was also to observe the effect of hypophysectomy on partial and total body irradiated rats and to evaluate the effect of testosterone on the leucocyte count in hypophysectomized and irradiated rats.

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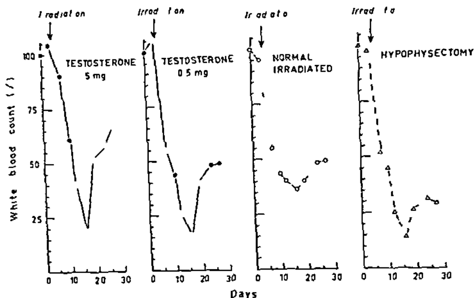


Fig 3 Effect of hypophysectomy and testosterone treatment on irradiated rats

upper body irradiation (from the xyphoid process up to and including the skull) and 16 rats were subjected to lower body irradiation (caudal to the xyphoid process) In each experiment of this set, half the number of rats had undergone upper body irradiation half the number of the lower body irradiated rats had been hypophysectomized and half the number not A group of hypophysectomized non irradiated rats served as control group

In each experiment the findings in the merely hypophysectomized and in the hypophysectomized and testosterone treated groups were compared with those in the simultaneously performed control experiments The differences between the treated rats and the control animals were examined by the Van Elteren's (1960) method of combining independent Wilco tests from the various experiments and the F test

Results

The results are presented in Figs 1 2 and 3 It may be seen that the recovery of the leucocyte count was faster in the testosterone treated groups than in the controls This difference was statistically significant Z = 0 00064 No

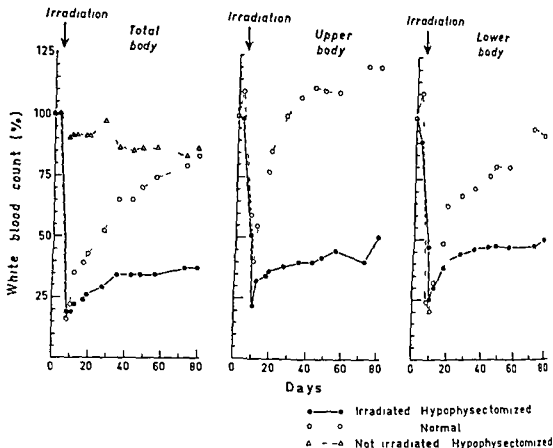


Fig 2 Effect of hypophysectomy on the white blood count in irradiated rats

were treated with testosterone and 25 served as controls Testosterone administration began a week prior to irradiation and was continued up to the end of the experiment

Each of the other two experimental groups consisted of 20 rats, 10 of which received upper body irradiation (from the xyphoid process up to and including the skull) and 10 rats lower body irradiation (caudal to the xyphoid process) In each experiment, half the number of the upper body irradiated and half the number of the lower body irradiated rats were treated with testosterone, the remainder serving as controls

In the fourth set of experiments, 40 rats were exposed to total body irradiation, of which 10 had been previously hypophysectomized and these received 5 mg testosterone daily, 10 had been hypophysectomized and got 0 5 mg testosterone, 10 had been hypophysectomized and recieved *no further treatment*, and 10 were not subjected to operation (controls)

The last set of experiments included 32 rats, 16 of which were exposed to

that irradiation of adrenalectomized rats provokes less drop and quicker increase in the leucocyte count than the irradiation of normal rats The present results indicate that the relative drop in the white blood count in hypophysectomized and normal irradiated rats is similar

Measurement of the response after irradiation disclosed that the quickest recovery was in the 5 mg testosterone treated rats followed by the 0 5 mg testosterone treated group and then the non operated group with the slowest recovery in the hypophysectomized rats It therefore appears that hypophysectomized rats have some impairment in their ability to recover after *irradiation* Testosterone is apparently able to correct this delay in the recovery of the leucocyte count It is not clear why hypophysectomized rats exhibit some delay in recovery It is obvious however, that hypophysectomy depresses *erythropoiesis* Testosterone has also the power to stimulate leucopoiesis in normal irradiated rats The present experiments have shown the same effect in hypophysectomized rats

This work suggests the advisability of administering chemotherapy before hypophysectomy in cases of mammary carcinoma If this is not feasible, testosterone treatment would seem to be indicated Further clinical trials are obviously required

SUMMARY

Normal and hypophysectomized rats were treated by total and partial body irradiation and testosterone propionate It would appear that some impairment occurs in the restoration of the leucocyte count following irradiation in hypophysectomized rats and that testosterone is able to correct this disturbance

ZUSAMMENFASSUNG

Normale Ratten und Ratten bei denen die Hypophyse exstirpiert war wurden mit Ganzkörper bzw partieller Bestrahlung und mit Testosteronpropionat behandelt Es scheint als ob bei den Tieren ohne Hypophyse die Normalisierung der Leukocytenzahl nach der Bestrahlung verzögert wurde und dass bei eine Verabreichung von Testosteron diese Storung korrigiert werden kann

RÉSUMÉ

Des rats normaux et des rats hypophysectomisés ont été traités par irradiation totale ou partielle du corps et par le propionate de testostérone Il semble que le retour à la normale du nombre des leucocytes après irradiation se fait plus difficilement chez les rats hypophysectomisés et que la testostérone peut remédier à cette perturbation

difference was noted between the treated and untreated groups in the maximum decrease in leucocyte count after irradiation

In the partial body treated groups the decrease in leucocyte count after irradiation was less, and its increase was more rapid in the upper body irradiated than in the lower body irradiated animals These differences proved however insignificant In both groups the rise in leucocyte count was more rapid in the testosterone treated than in the corresponding untreated group

The following points were investigated in the last two sets of experiments (1) the initial drop in the leucocyte count after irradiation, (2) the increase in leucocytes between the lowest count and that present 2 weeks after irradiation, and (3) the difference between the pre irradiation value and that at the end of the experiment

The initial absolute drop in the leucocyte count was greater in the hypophysectomized and irradiated rats than in the non operated irradiated group, P = 0 001 Measurement of the relative decrease revealed however no difference between the groups This discrepancy is due to the fact that the pre irradiation leucocyte count in the hypophysectomized rats was higher In all the groups exposed to total body irradiation, the difference between the lowest count and that obtained two weeks later indicated that it was least in the irradiated operated group and increased in the other groups according to the following order non operated and irradiated, irradiated plus testosterone 0 5 mg, hypophysectomized and irradiated, and testosterone 5 mg *All these differences were statistically significant, P = 0 01 When the difference* between the pretreatment value and that obtained at the end of the experiment was compared in the four groups undergoing total body irradiation, it was evident that the smallest difference was in the operated plus testosterone 5 mg group, followed by the group of operated plus testosterone 0 5 mg, the non operated, and lastly the operated group The differences between the groups were significant, P = 0 01 In the partial body irradiated rats there was a quicker recovery in the leucocyte count for the upper body irradiated than in the lower body irradiated group In the hypophysectomized upper or lower body irradiated rats, the leucocyte count recovery was slower *than in the corresponding control*

Discussion

Hypophysectomy in carcinoma of the breast in human subjects is a well established method of treatment However, it is not known if the white blood count reacts differently to radiotherapy and chemotherapy in hypophysectomized cases compared *to others* Hochman *et coll* (1961) have reported

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EFFECTS OF RADIATION DAMAGE TO BONE MARROW ON SUSCEPTIBILITY OF CHICKS TO ERYTHROLEUKEMIA VIRUS

by

C. H. CHI and B. LAGERLÖF

Studies of fowl and murine virus-induced leukemias indicate that several host factors are responsible for the susceptibility. Increasing immunologic maturity of the host and increasing cellular differentiation together with decreasing proliferative activity of the target cells are associated with decreasing susceptibility to virus action in some systems (LAGERLÖF & SUNDELIN 1963). In murine leukemia systems the response of the animal to the virus can be markedly enhanced by roentgen irradiation or by urethane which cause damage and subsequent regeneration of the thymus, the target organ of the virus (KAPLAN 1967, HARAN-GHERA & KAPLAN 1964).

The present investigation was undertaken with a view to determine whether the pathogenic effect of the fowl erythroleukemia virus can be altered by modifying the cellularity and the degree of cellular differentiation of the target, i.e. the bone marrow. Bone marrow changes were produced by exposing the chicks to whole body irradiation. The sequential changes in the bone marrow after irradiation were followed in a pilot study. Based on this experiment, a study was

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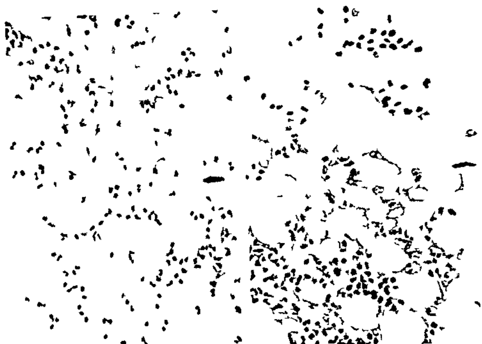


Fig 1 Acute irradiation damage of bone marrow at 4 days Edema and few viable erythrocytes (centre) in the necrotic marrow Hematoxylin eosin ×250

Fig 2 Acute irradiation damage with edema and cellular necrosis 4 days after irradiation Persisting erythropoietic activity in some sinusoids (bottom) Hematoxylin eosin ×300

been recorded in tables In addition, the susceptibility to the virus has been calculated according to

$$\sum \frac{1}{t} / N$$

where t is the latent period from virus inoculation to death and N is the corrected number of virus-inoculated chicks

Experimental groups Chicks were exposed to a single dose of 600 rad in one experiment (1) intended for the evaluation of radiation damage to the bone marrow The chicks were killed by decapitation 4 8, 12 and 20 days after irradiation and all marrow in both femora and tibiae was collected separately for histologic examination Four to six untreated normal chicks of corresponding ages furnished the control material

performed on the pathogenic effect of the erythroleukemia virus inoculated in the chicks, in the successive phases of post irradiation damage and regeneration of the bone marrow.

Material. Random bred white Leghorn *chicks* (Vanhammar, Vansbro) were used throughout. They were kept in artificially heated cages with free access to commercial chick feed and water; irradiated and non irradiated chicks were kept in separate cages but otherwise the conditions were the same.

The properties of the erythroleukemia *virus* and the disease evoked by it have been described in detail earlier (LAGERLÖF 1960). The source of the virus was a lyophylized pool of medium from cultures of erythroleukemic bone marrow, diluted to the original volume with distilled water. The dose was 0.2 ml intravenously.

Irradiation. The chicks were exposed to a single dose of 600 rad unfiltered ^{60}Co, the exposure time being 19 minutes and the source target distance 150 cm. The irradiation resulted in about 10 per cent mortality within the first two days. The preliminary pilot studies had indicated that this dose caused considerable damage to the marrow in spite of the low mortality rate.

For *bone marrow biopsy* the right femur was exposed under general anesthesia, and a hole of 2 mm diameter was drilled through the cortex of the bone into the medullary cavity. A piece of bone marrow, about 5 mm in length, was aspirated through a needle of 1 mm diameter. The hole was covered with muscular tissue and the operation area closed with silk.

Histologic examination. Bouin's fixative was used for the biopsy material of bone marrow and other tissues collected for histologic examination. Ordinary paraffin sections were prepared and stained with hematoxylin eosin.

All histologic sections were coded and the examination was made without knowledge of the time of the irradiation treatment. The control marrows were also included, as coded histologic sections, in the experimental material.

Necrosis and edema, indicative of recent damage, were registered as well as increased fat infiltration with decreased cellularity and signs of erythroid or myeloid regeneration. All these findings were semi quantitatively registered according to a 4+ scale where 0 denoted normal findings, 1 or 2+ slight to moderate changes, and 3 or 4+ severe changes.

The obtained biopsy material was sometimes too small to permit a reliable histologic examination. These specimens were excluded when calculating the virus activity figures in the various groups in Table 2.

Calculation of virus activity. The number of chicks dying from leukemia versus number of virus inoculated chicks corrected for intercurrent deaths, have



Fig 5 Aplastic bone marrow 0 days after irradiation Hematoxylin-eosin ×350

Fig 6 Low power view Persistent edema and patchy necrosis of bone marrow 20 days after irradiation Hematoxylin-eosin ×100

Results

Evaluation of radiation damage to bone marrow

Four days after irradiation The changes at microscopy of the bone marrow 4 days after irradiation with 600 rad were uniform in type although the degree differed All samples exhibited moderate to marked necrosis haemorrhage and edema associated with hypocellularity and marked depression of the hematopoietic activity (Fig 1) Slight erythropoietic activity was evident in some areas Fig 2)

Eight days after irradiation Necrosis of the bone marrow was still a common finding 8 days after irradiation Haemorrhage and edema were present to about the same degree as in the 4-day group The changes were generally associated with increased fat infiltration in the marrow and more or less complete aplasia in large areas. Usually only the peripheral parts of the marrow presented hematopoietic activity (Fig 3) The marrow from one of the four chicks exhibited

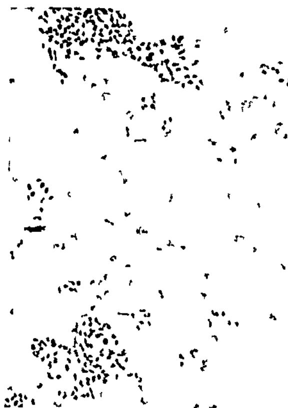


Fig 3 Hypoplastic bone marrow with increased fat content 8 days after irradiation Slight myeloid activity with two sinusoids presenting moderate erythropoietic activity Hematoxylin eosin ×250



Fig 4 Sinusoid with moderate erythropoietic activity 12 days after irradiation Slight myeloid activity in the extrasinusoidal tissue is also evident Hematoxylin eosin ×350

Groups of twelve 1 day old chicks were in another experiment (2) exposed to 600 rad and bone marrow biopsy was performed 2, 8 and 20 days after irradiation Following biopsy, the chicks were inoculated with erythroleukemia virus Histologic examination of the bone marrow, spleen and liver was performed in all the chicks that died of leukemia or were killed at the termination of the experiment, 60 days after inoculation Corresponding groups of non irradiated chicks constituted the control material The control groups were virus inoculated at the same time as the experimental groups

All the groups were kept for 2 months and then the remaining chicks were killed and examined

Intercurrent deaths Five out of a total of 72 chicks, in the experimental and control groups, died intercurrently before leukemia had developed These five chicks were excluded from any further calculations

Table 2

Correlation of erythroleukemia virus activity with the degree of radiation marrow damage (A) and evidence of erythroid regeneration (B)

	Number of dead versus number of inoculated	$\sum \frac{1}{i} / N$
A		
Irradiated chicks with advanced marrow damage (3 and 4+)	4/13	0.075
Irradiated chicks with slight marrow damage (1 and 2+)	17/21	0.092
B		
Irradiated chicks with histologic evidence of erythroid regeneration	17/25	0.062
Irradiated chicks without histologic evidence of erythroid regeneration	4/9	0.078
Nonirradiated control chicks	22/33	0.063

The incidence of leukemia at corresponding ages was almost *identical in the* experimental groups and the control groups. The susceptibility of the chicks as *calculated* according to

$$\sum \frac{1}{i} / N$$

was identical *in the experimental* groups and the control groups at 2 days and 20 days after irradiation. At 8 days the control group had a *slightly higher* susceptibility.

The biopsies revealed that these experimental groups differed from the above mentioned groups by having greater intra group *variations* of radiation damage. Thus some of the chicks that were inoculated with virus 20 days after irradia*tion had* persistent widespread cellular necrosis of the marrow or aplasia with marked fatty infiltration (Fig. 6). *Placing the birds* according to the presence of severe marrow damage and advanced hypocellularity into one group (3 and 4+) and those according the presence of slight to moderate necrosis or hypocellularity into another (1 and 2+) *irrespective* of the time of virus-inoculation gave the figures recorded *in* Table 2.

The chicks with severe marrow damage histologically classified as 3 or 4+ had markedly reduced *susceptibility for the* virus and only four out of thirteen chicks developed leukemia. Of the twenty-one chicks with *slight or* moderate *marrow* damage seventeen developed leukemia: this is an incidence higher than

Table 1

Erythroleukemia virus activity in irradiated and non irradiated chicks

Days between irradiation and virus inoculation	Radiation plus virus		Virus only	
	Number of dead versus number of inoculated	$\sum \frac{1}{t} / N$	Number of dead versus number of inoculated	$\sum \frac{1}{t} / N$
2	7/10	0.066	7/10	0.070
8	8/12	0.057	8/11	0.071
20	7/12	0.047	7/12	0.056
	22/34	0.056	22/33	0.065

slight granulopoietic activity and the other samples had mild erythropoietic activity

Twelve days after irradiation The marrow in this group was regularly fatty and hypocellular, and necrosis was only slight compared with earlier groups Hematopoietic activity was limited to the periphery where most samples had slight to moderate erythropoietic activity (Fig 4) One of the four birds also exhibited moderate granulopoietic activity

Twenty days after irradiation The marrow in this group was usually hyper plastic, with moderate to marked erythropoietic and granulopoietic activity The fat content of the marrow compared with that of the abovementioned groups and the controls was reduced One of the four chicks had changes that deviated considerably from the others This chick had a hypoplastic fatty marrow with evidence of slight erythroid and myeloid cell proliferation (Fig 5) No edema or cellular necrosis were seen in the marrow

The bone marrow damage and regeneration were uniformly distributed The marrow of both femora and tibiae was essentially similar in each chick A biopsy sample of the femur marrow was considered to represent the radiation damage to the whole marrow in the following experiments on the combined effects of ir radiation and erythroleukemia virus

Combined treatment of chicks with radiation and erythroleukemia virus The combined treatment with radiation and erythroleukemia virus in the control chicks gave overall results similar to those in which treatment was with virus alone (Table 1)

Table 2

Correlation of erythroleukemia virus activity with the degree of radiation marrow damage (A) and evidence of erythroid regeneration (B)

	Number of dead versus number of inoculated	$\sum \frac{1}{t} / \lambda$
A		
Irradiated chicks with advanced marrow damage (3 and 4+)	4/13	0.025
Irradiated chicks with slight marrow damage (1 and 2+)	17/21	0.092
B		
Irradiated chicks with histologic evidence of erythroid regeneration	17/25	0.062
Irradiated chicks without histologic evidence of erythroid regeneration	4/9	0.078
Nonirradiated control chicks	22/33	0.063

The incidence of leukemia at corresponding ages was almost identical in the experimental groups and the control groups. The susceptibility of the chicks as calculated according to

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was identical in the experimental and the control groups at 2 days and 20 days after irradiation. At 8 days the control group had a slightly higher susceptibility.

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The chicks with severe marrow damage histologically classified as 3 or 4+ had markedly reduced susceptibility for the virus and only four out of thirteen chicks developed leukemia. Of the twenty-one chicks with slight or moderate marrow damage seventeen developed leukemia; this is an incidence higher than

in the control chicks The lower susceptibility correlated with severe marrow damage is also evident from the calculated activity values according to

$$\sum \frac{1}{t} \Big/ N$$

where both the latent periods and incidence influence the values It is also obvious from Table 2 that erythroid regeneration in the radiation damaged marrow contributes to the susceptibility of the chicks to the virus Chicks with evidence of erythroid regeneration in the marrow were much more susceptible than chicks without evidence of erythroid regeneration

Histologic examination of the irradiated and virus-inoculated chicks, dying or killed in the terminal stage of erythroleukemia, revealed persistent bone marrow necrosis in four chicks, with only slight leukemic infiltration despite heavy leukemic infiltration in other organs (Figs 7 and 8)

Discussion

The results obtained clearly demonstrate that advanced cellular necrosis of the bone marrow produced by a single dose of irradiation inhibits the development of erythroleukemia (Table 2) The most likely cause of this inhibitory effect is that the target cells for the virus are damaged and reduced in number The marrows with advanced necrosis contained very few viable cells scattered throughout its highly edematous marrow There was a striking difference in susceptibility to the virus between this group and the one with only slight or moderate damage The latter group had an increased susceptibility also in comparison with unirradiated control groups This is interpreted as being due to rapid regeneration whereby the marrow will contain actively proliferating erythroid cells which are the target of the virus The difference in susceptibility to the virus might thus be explained by the shortage or abundance of immature proliferating erythroid cells This hypothesis was checked by grouping the experimental chicks according to histologically demonstrable erythroid proliferation in one group and absence of erythropoietic activity in another group (Table 2, group B) The erythropoietically active group was more susceptible to the virus than the inactive group The activity values were not as high as in the group classified as having slight radiation damage The difference is small, however, and largely due to longer latent periods in the group classified as presenting evidence of erythroid regeneration

The total leukemia incidence is almost identical in the irradiated and the non irradiated groups, and only shorter latent periods increase the activity values in



Fig 7 Fat marrow containing scattered foci of leukemia cells in a chick dying of fulminant erythroleukemia following exposure to radiation 17 days previously Hematoxylin eosin ×350

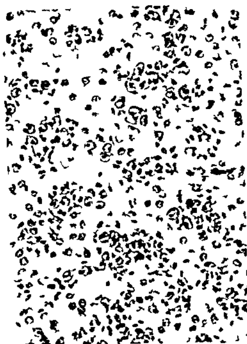


Fig 8 Liver from the same case as in fig 7 Heavy leukemic infiltration with sinusoids distended by leukemia cells Hematoxylin eosin ×350

the unirradiated group It is thus obvious that the decrease in susceptibility dependent upon radiation damage is compensated for by the increased susceptibility of the chicks with only slight marrow damage

The dose of virus administered has been the same in all the groups The short latent periods from inoculation to death indicate that the virus preparations have been very active No further attempts have been made in the present study to determine whether changing the virus dose would influence the response of the irradiated marrow

The results obtained support the hypothesis that the pathogenic effect of this oncogenic virus is primarily dependent upon the presence of specific target cells Whether the increased susceptibility reflects only the increased number of actively proliferating erythroid cells or whether irradiation has also caused a qualitative change in the cells cannot be settled by the results so far obtained It is interesting to note that at the terminal stage of the leukemia only light

leukemic infiltration was present in the fatty or edematous marrow of some of the irradiated chicks, despite heavy infiltration in other organs. Radiation damage obviously reduced the capacity of the marrow not only to develop leukemia but also to support the growth of neoplastic cells.

Acknowledgement

The investigation was supported by grants from the Swedish Cancer Society and the Therese and Johan Andersson's Foundation and by a grant to one of the authors (C. H. Chi) from the Swedish International Development Authority. The skilful assistance rendered by Miss Yvonne Kock and by Mr Ejnar Jonsson of Radiumhemmet is gratefully acknowledged.

SUMMARY

Groups of chicks were inoculated with erythroleukemia virus 4, 8 and 20 days after exposure to 600 rad ^{60}Co radiation. Biopsy material from the femur marrow was obtained immediately prior to the virus inoculation. The incidence of leukemia and the latent periods to death of the chicks were recorded and a comparison is made between the groups of irradiated plus virus inoculated chicks and, respectively, only virus inoculated chicks. The results support the view that the pathogenic effect of the virus can be modified by varying the number of target cells and their differentiation.

ZUSAMMENFASSUNG

Gruppen von Küken wurden mit 600 rad ^{60}Co bestrahlt und 4, 8 und 20 Tage nach der Bestrahlung mit dem Erythroleukämievirus geimpft. Unmittelbar bevor der Einimpfung wurde Biopsiematerial aus dem Femurmark genommen. Die Untersuchungsergebnisse mit Hinsicht auf das Auftreten von Leukämie und die Latenzperioden bis zum Tode der Küken werden für die beiden Gruppen von bestrahlten und Virus-injizierten Küken bzw. nur Virus-injizierten Küken in Relation gestellt. Die Ergebnisse deuten darauf hin, dass der pathogene Effekt des Virus durch Veränderungen in der Anzahl von Target-Zellen und in ihrem Differenzierungsgrade modifiziert werden kann.

RÉSUMÉ

Des groupes de poussins ont été innoculés avec le virus de l'érythroleucémie quatre, huit et vingt jours après avoir été exposés à une dose de 600 rad de ^{60}Co. Les poussins qui sont morts de leucémie ont été examinés histologiquement. Les auteurs ont comparé la fréquence de la leucémie et la *période de latence jusqu'à la mort des poussins* chez ceux qui avaient reçu l'irradiation et le virus et chez ceux qui n'avaient reçu que le virus. Les résultats de cette expérience viennent à l'appui de l'hypothèse que l'effet pathogène du virus peut être modifié au moyen de changements dans le nombre de cellules cibles et dans leur degré de différenciation.

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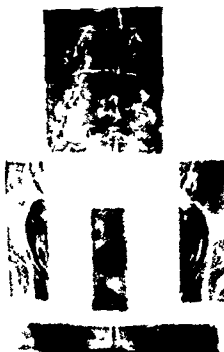
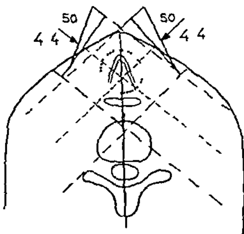


Fig 1 Narrow beam exposures in one and the same film used for locating carcinoma of the pel is and for pelvimetry Contrast medium is seen in the lymph nodes





Figs 1 3 Field check in a case of laryngeal carcinoma (left) and position of fields (right)

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CLINICAL APPLICATIONS OF A FIELD POSITIONING AND SIMULATING STAND

by

JOHN JOHANSSON, BENGT ROSENGREN and BENGT TJERNBERG

The field positioning and simulating stand described in a previous paper by JUNG, LARSSON, ROSENGREN et coll has been applied clinically in connection with the planning of treatment with high energy radiations as well as for field checking

Conventional roentgen stands are built to enable projections to be set up that provide the best diagnostic opportunities, while therapeutic stands are constructed with a view to achieving the optimal dosage distribution The design of the simulator stand makes it possible to reproduce the angles used with therapeutic machines under identical conditions and with the correct focus skin distance, herein lie the constructive peculiarities of simulators

In *treatment planning* it is possible to localize, by means of a variety of projections, usually with the central ray horizontal or vertical, and to mark out on the patient s skin the positions of vertebrae and other parts of the skeleton, organs that can be filled with contrast medium, e g the bladder (for bladder tumours), and regions that at operation have been marked by indicators, usually in the thorax or abdomen

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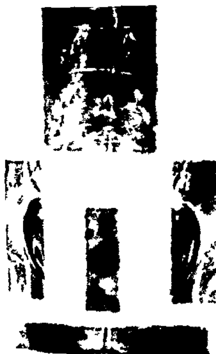
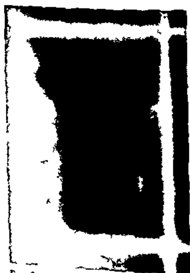
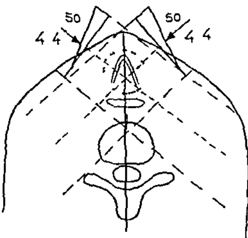


Fig 1 Narrow beam exposures in one and the same film used for locating carcinoma of the pelvis and for pelvimetry Contrast medium is seen in the lymph nodes





Figs 2 and 3 *Field check* in a case of laryngeal carcinoma (left) and position of fields (right)

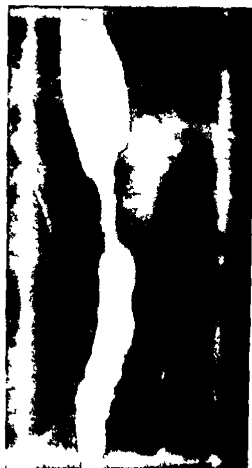


Fig 4

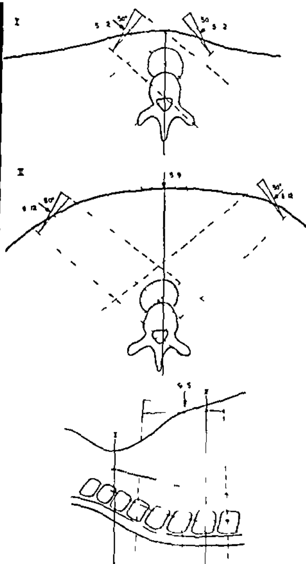


Fig 5

Figs 4 and 5 Field check in a case of oesophageal carcinoma (left) and position of the fields in different planes (right)

Positioning is possible also if the region to be treated cannot be rendered visible by any of the techniques just mentioned since in such cases the region to be irradiated can be marked out by guidance of its known relationships to various skeletal landmarks Certain skeletal details in the pelvis may for example in gynaecologic treatment be employed as markers during the planning stage

It is most important that organs or parts of organs that should not be exposed to unnecessary radiation can readily be located A good example is the determina



Fig 6

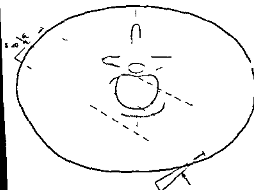


Fig 7

Figs 6 and 7 Field check in a case of embryonic tumour of the testis undergoing irradiation of the lumbar lymph nodes (left) and position of the field (above)

tion of the position of the spinal cord When lymph nodes in the hilar regions of the kidneys are to be treated it is possible to avoid irradiation of the kidneys themselves by localizing them by means of urography performed during the examination with the simulator

Positioning so-called indication is commonly carried out by first obtaining a survey view of the general region and then stepping down to narrow slits so that in principle merely the central ray is used By moving the patient sideways or vertically in the narrow beam the margins of the region to be irradiated may then be marked out on the patient and the measurements transferred directly to the dosage plan If a roentgen film is placed under or beside the patient and several narrow beam exposures are made on the same film measurements may be obtained directly from the roentgen image without consideration of enlargement factors Such a method used for localizing carcinoma of the pelvis in women is illustrated in Fig 1

Field checks are most important when small fields are employed and accurate positioning is essential, e g in cases of laryngeal carcinoma for which the vocal cord region must be in the middle of the region to be irradiated so that irradiation of the spinal cord is avoided An example of this appears in Figs 2 and 3 Experience has shown that it may be difficult to position fields when the longitudinal axis of the tumour region forms an angle with the horizontal plane, e g in oesophageal carcinoma The pendulum axis as well as the position of the collimator must then be angled The field positioning and simulator stand makes this comparatively simple, a field check of this type is shown in Figs 4 and 5 It is also difficult to position the region to be treated so that the spinal cord is avoided in irradiation of the lumbar lymph nodes, e g in cases of embryonic tumours of the testes A field check in such a case appears in Figs 6 and 7 Checking is usually made with an image intensifier and then, if desirable, the observations are documented on a roentgen film placed in the cassette holder on the image intensifier

In conclusion it may be stated that the simulator has been found to be indispensable both for dose planning and field checking

SUMMARY

The clinical applications of a field positioning and simulating stand are described

ZUSAMMENFASSUNG

Die praktische Anwendbarkeit eines Bestrahlungssimulators fur Feldlokalisierung wird besprochen

RÉSUMÉ

Les auteurs décrivent les applications cliniques d un statif de mise en place des champs et de simulation

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FROM THE RADIUM CENTRE FOR JUTLAND (DIRECTOR PROF S YAAE), AARHUS
DENMARK

INTRACAVITARY THIOTEPA IN MALIGNANT PLEURAL AND PERITONEAL EFFUSIONS

by

A P ANDERSEN and H BRINCKER

A number of methods for controlling the exudation in serous cavities, in the palliative treatment of cases of effusions of malignant origin have been introduced during the past two decades Resort had previously to be made to fre *quent* paracenteses sometimes supplemented by roentgen irradiation to large thoracic or abdominal fields Radiotherapy frequently caused severe side reac *tions* and its effect was often poor Hormonal therapy was only occasionally beneficial

Intracavitary application of radioactive isotopes was introduced in 1945 by MULLER who used ^{65}Zn and later (1950) ^{198}Au Numerous reports have since been published inter alios by DENNIS et coll (1956), HANSEN & HAUG (1960) and LAMBRETHSEN & SELL (1961) on favourable results with ^{198}Au the exuda tion ceasing or being reduced *in 50 to 70* per cent of the cases However this treatment has the drawback of requiring specially trained staff which will be exposed to a certain amount of radiation even with the best apparatus Further more it is rather costly and not suited for ambulatory use

CLADIO & PERCESEPE (1958) employed prednisolone intrapleurally in a

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Table 1

Therapeutic results of intrapleural and intraperitoneal instillation of various cytostatics

Authors	Agent	Number of cases	Favourable effect		Side effects
Bateman et coll	Thiotepa	24	16/24	66.7 %	
Groesbeck & Cudmore	Thiotepa	27	20/27	74.1 %	Bone marrow depression
Goodman et coll	KC 33	60	33/60	55.0 %	
Weisberger et coll	HN2	41	26/41	63.4 %	Bone marrow depression local pain
Rieve & Myhre	HN2	13	11/13	84.6 %	Nausea
Suhrland & Weisberger	5 fluorouracil	52	29/52	55.8 %	Bone marrow depression
Gellhorn et coll	Quinacrine	31	14/31	45.2 %	Fever, local pain

Table 2

Distribution by primary tumour, sex and site of effusion

Primary tumour	Number of cases			Number of treated effusions		
	Males	Females	Total	Pleural cavity	Peritoneal cavity	Total
Breast cancer	0	16	16	14	2	16
Ovarian cancer	0	35	35	5	34	39
Genital cancers (ovarian cancer excl.)	3	6	9	3	6	9
Gastro intestinal cancer	2	1	3	1	2	3
Cancer of the lung	3	5	8	8	0	8
Malignant lymphomas	3	3	6	8	0	8
Other cancers	6	3	9	3	6	9
Total	17	69	86	42	50	92

group of 20 cases with malignant pleural effusions. The treatment caused no complications and produced a positive result in 70 per cent of the cases.

Obliteration of the pleural cavity has also been employed in the treatment of malignant pleural effusions. Hauer et coll. (1960) and Starkey (1964), for instance, used intrapleural talc poudrage, while Jensik et coll. (1963) performed pleurectomy. The results of these therapeutic methods appear to have been extremely satisfactory, although it must have been unfortunate that such pa

Table 3

Effect of intracavitary thiotepa in relation to primary tumour in the various groups

Primary tumour	Symbols for groups used in the assessement see pp 372—373					
	++ & +		(++) & (+)	0	?	Total
Breast cancer	1	26 (47 2)	8	4	3	16
Ovarian cancer	6		11	12	10	39
Cancer of the lung	1		1	0	6	8
Malignant lymphomas	2		1	2	3	8
Other cancers	2		1	7	11	21
Total	12	34 (37 0)	22	25	33	92

tients often in a poor general condition had to be exposed to an operative procedure

KARNOFSKY et coll (1948) reported that they had obtained regression of recurrent pleural effusion following the intracavitary instillation of nitrogen mustard (HN2) in a case of bronchogenic carcinoma Since then, other alkylating cytostatics have been tried and have included in addition to HN2 KC-33 (N hexamethylene N ,N diethylene thiophosphoramide) and thiotepa (N N N triethylene thiophosphoramide) Other agents have also been administered e g the pyramidine analogue 5 fluorouracil (SUHRLAND & WEISBERGER 1965) and the antimalarial quinacrine (GELLHORN et coll 1961)

The results of treatment with the mentioned substances in a varying series of malignant effusions are presented in Table 1 The results appear to be similar to those obtained with ^{198}Au Direct comparison of the various substances and series is however hardly possible since the assessment criteria often differ and the number of unassessable cases varies

Treatment with cytostatic agents has considerable advantages over the other therapeutic methods mentioned Cytostatics are easy to administer they are also relatively cheap and require no special apparatus or specially trained staff The side effects are generally mild and usually restricted to bone marrow depression However HN2 may produce local pain and nausea, and quinacrine may also induce fever These two substances should therefore be given only to in patients while the others are well suited for the out patients clinics

Material and therapeutic procedure The material comprises 86 cases treated during the period 1956—1967 and was made up of sixty eight from the Radium

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Authors	Agent	Number of cases	Favourable effect		Side effects
BATEMAN et coll	Thiotepa	24	16/24	66 7 %	
GROESBECK & CUDMORE	Thiotepa	27	20/27	74 1 %	Bone marrow depression
GOODMAN et coll	KC 33	60	33/60	55 0 %	
WEISBERGER et coll	HN2	41	26/41	63 4 %	Bone marrow depression local pain
REEVE & MYHILL	HN2	13	11/13	84 6 %	Nausea
SUHRLAND & WEISBERGER	5 fluorouracil	52	29/52	55 8 %	Bone marrow depression
GELLHORN et coll	Quinacrine	31	14/31	45 2 %	Fever local pain

Table 2

Distribution by primary tumour, sex and site of effusion

Primary tumour	Number of cases			Number of treated effusions		
	Males	Females	Total	Pleural cavity	Peritoneal cavity	Total
Breast cancer	0	16	16	14	2	16
Ovarian cancer	0	35	35	5	34	39
Genital cancers (ovarian cancer excl)	3	6	9	3	6	9
Gastro-intestinal cancer	2	1	3	1	2	3
Cancer of the lung	3	5	8	8	0	8
Malignant lymphomas	3	3	6	8	0	8
Other cancers	6	3	9	3	6	9
Total	17	69	86	42	50	92

group of 20 cases with malignant pleural effusions The treatment caused no complications and produced a positive result in 70 per cent of the cases

Obliteration of the pleural cavity has also been employed in the treatment of malignant pleural effusions HAUPT et coll (1960) and STARKEY (1964), for instance, used intrapleural talc poudrage, while JENSIK et coll (1963) performed pleurectomy The results of these therapeutic methods appear to have been extremely satisfactory although it must have been unfortunate that such pa

Table 5

Other simultaneous treatments in groups (++) and (+)

	Group (++)	Group (+)	Total
Relevant roentgen therapy	3		3
Hormone and/or castration therapy	4	3	7
Instillation of Au		2	2
Systemic cytotoxic therapy	4	2	6
Intracavitary thiotepa at first paracentesis	2	2	4
Total	13	9	22

been instituted less than 2 months prior to the thiotepa therapy or else thiotepa was administered at the very first paracentesis

0 indicates an unchanged frequency of punctures and/or fluid production

? indicates unassessable cases due to (1) death within 2 months of the first administration of thiotepa (2) prophylactic treatment and (3) deficient data

Other simultaneous treatments consisted in (A) relevant radiotherapy (B) hormone therapy with or without castration and (C) systemic cytotoxic treatment

Results

The results of the treatment in relation to the primary tumour are given in Table 3 The majority of the cases of mammary carcinoma pulmonary carcinoma and malignant lymphoma had pleural effusions while the others had mostly peritoneal effusions (cf Table 2)

In Table 4 the relationship between the therapeutic effect and the site of effusion is illustrated The thirty three unassessable cases were almost without exception in a wretched state and survived for less than two months after thiotepa therapy Twenty two received some other simultaneous treatment or else intracavitary thiothepa at the very first paracentesis They have therefore been classified as (++) or (+) The numerical distribution of these groups is listed in Table 5

The therapeutic results for the entire material as well as for pleural and peritoneal effusions separately are set out in Table 6 in relation to other materials treated with intracavitary application of alkylating agents In these other materials unassessable cases do not appear to have been excluded and only GROTSBECK & CUDMORE (1962) give any detailed account of other concomitant treatment If unassessable cases are excluded a favourable effect

Table 4

Effect of intracavitary thiotepa in relation to site of effusion

Effect*	Pleural effusions			Peritoneal effusions			Total		
++	2	5	18 (42 9 %)	4	7	16 (32 0 %)	6	12	34 (37 0 %)
+	3			3			6		
(++)	8	13		5	9		13	22	
(+)	5			4			9		
0	8			17			25		
?	16			17			33		
Total	42			50			92		

* For explanation of symbols see pp 372—373

Centre in Aarhus and eighteen from the Radium Centre in Odense The distribution, by primary tumour, sex, and site of effusion, is indicated in Table 2 The group of 35 cases with ovarian carcinoma includes eleven cases in which only the ascitic fluid had been examined histologically, but the clinical course had been typical of ovarian carcinoma The number of treated effusions amounts to 92 since a few patients had effusions in two or three sites Seventy seven of the patients were in the age group 40 to 70 years, six being older and three younger At the time when the analysis was closed (June 1st, 1967) seventy three patients had died, while thirteen were alive and attending ambulatory control No patient had been lost to follow-up

The therapeutic procedure was as follows After adquate paracentesis, 45 mg thiotepa dissolved in 10 ml water were instilled direct through the same needle The dose was however sometimes 30 mg into the pleural and 60 mg into the peritoneal cavity Two children received a small dose adapted to body weight

Assessing the results, the following symbols were used

++ No paracentesis for more than 4 months (regardless of subsequent intractable recurrence)

+ No paracentesis for from 2 to 4 months, or a double interval between the punctures

(Within groups ++ and + any simultaneous treatment was started more than 2 months before the thiotepa therapy, and the frequency of punctures prior to this treatment had been less than 2 months)

(++) & (+) Same criteria as above but other simultaneous treatment had

Table 7

Effect of intracavitary thiotepa in relation to nature of effusion

Effect	Haemorrhagic effusions	Serous effusions	Chylous effusions	Unknown	Total
++ & + (++) & (+)	13	21			34
0	4	21			25
	13	18	1	1	33
Total	30	60	1	1	92

For explanation of symbols see pp 372—373

cases received two instillations Only four cases had from 3 to 11 instillations, but all responded to the first or second treatment later instillations being given for recurrences, generally with good effect Eleven of the twenty five cases that failed to respond received from 3 to 6 instillations A favourable effect if any, may thus be expected at least after the second instillation If a case has shown no response at that time, the chances of a response to thiotepa are slight

Fifty seven of the eighty six cases exhibited adequate haematologic control during the treatment Thirty five developed mild to moderate leukopenia and/or thrombocytopenia of a transient nature but none had signs of serious bone marrow depression No relationship was found between a positive response and signs of bone marrow depression which thus does not appear to be essential for a favourable therapeutic result

As already mentioned seventy seven of the subjects were in the 40 to 70 year age group no definite difference was observed in the therapeutic results in those who were in their forties fifties or sixties

Among the unassessable cases, thirty of which survived for less than two months after the thiotepa therapy, there was a preponderance of histories of less than two months duration while among those with a favourable response to the treatment the majority of histories exceeded a year Most of the unassessable cases were not however at the time of the treatment in such a poor general condition that a rapidly fatal course could have been predicted It was a characteristic finding that while only about a quarter of the cases in the groups of breast and ovarian carcinoma were unassessable, about half the number of those with growths in other sites were unassessable

Out of the remaining cases twelve patients survived for from 2 to 4 months,

Table 6

Effect of intracavitary thiotepa compared with other materials treated with alkylating agents

Site of effusion	Effect**	Incl unassessable	Excl unassessable	Average of other materials treated with alkylating agents
Pleural + peritoneal	++ & +		12/37 (32 4 %)*	
	++ & + and (++) & (+)	34/92 (37 0 %)	34/59 (57 6 %)	106/165 (64 2 %) Ref 1 6 7 15 and 19
Pleural	++ & +		5/13 (38 5 %)*	
	++ & + and (++) & (+)	18/42 (42 9 %)	18/26 (69 2 %)	42/61 (68 9 %) Ref 1 7 and 19
Peritoneal	++ & +		7/24 (29 2 %)*	
	++ & + and (++) & (+)	16/50 (32 0 %)	16/33 (48 5 %)	20/31 (64 0 %) Ref 1 7 and 19

* Group (++) & (+) also excluded

** For explanation of symbols see pp 372—373

of the treatment was obtained in 57 6 % of the present cases This corresponds to an average of 64 2 % in other materials But if the unassessable cases are included, a favourable result was obtained in 37 0 % of the present cases Furthermore, if the therapeutic results are accepted as definitely positive only in cases that received no other simultaneous treatment, there is a favourable result in only 32 4 % of the cases after exclusion of the unassessable cases and the cases receiving other simultaneous treatment The corresponding values for pleural and peritoneal effusions respectively are evident from Table 6

Table 7 indicates the relationship between the nature of the effusion and the therapeutic result An equally large number of cases (21/21) with serous effusions responded favourably or not at all It will be seen that with haemorrhagic effusions a favourable response was obtained in 13 out of 17 cases These values indicate the possibility of a better therapeutic result in this condition

We also investigated the relationship between the therapeutic result and the number of instillations Twenty three of the thirty four cases that responded well to the treatment needed only one instillation of thiotepa, while seven

Similarly the results appear to be better in the treatment of pleural than of peritoneal effusions This has already been pointed out by BATEMAN et coll (1955), GROESBECK & CUDMORE (1962), and SUHRLAND & WEISBERGER (1965)

Conclusion

Treatment of malignant effusions with intracavitary thiotepa is of indubit able value in quite a large proportion of cases It is devoid of risk to the patients as well as to the staff and entails so little discomfort and so few side effects that its selection for the first therapeutic attempt appears reasonable The treatment seems to be most effective in mammary or ovarian carcinoma of long duration and in cases of haemorrhagic effusions Pleural effusions appear to react better than peritoneal effusions If the case does not respond by a reduction in the effusion after two instillations of thiotepa other methods should be tried

Acknowledgement

The authors wish to thank P Bjerre HANSEN and E LAMBRETHSEN for the loan of the case sheets

SUMMARY

Thiotepa injections into the pleural and peritoneal cavities were given in a series of 86 cases The treatment had a favourable *effect in* 37 *per cent* and if unassessable cases are ex cluded in 57 6 *per cent of the cases The greatest* chance *of* response had cases with mammary or ovarian carcinoma *of long duration* and cases with haemorrhagic effusions

ZUSAMMENFASSUNG

Thiotepa Inj ktionen in die *Pleurahohle* und die Peritonaalhohle wurden in 86 Fallen durchg fuhrt Eine gunstige *Wirkung* der Behandlung wurde in 37 Prozent der Falle erzielt und wenn man zweifelhafte Falle *ausschliesst in* 57 6 Prozent Die beste Voraussetzung fur einen guten Erfolg erboten Falle *von* andauernden Brust und Ovarial Karzinomen und Falle mit hämorrhagischen Ergussen

RÉSUMÉ

Une série de 86 malades *ont été traités* par injection de thiotepa dans les cavités pleurale et peritonéale Ce traitement a eu un effet favorable dans 37 pour cent de l ensemble des cas et si on él mine les cas *impossibles à juger* il a eu un effet favorable dans 57 6 *pour* cent des cas Les meilleures chances *d effet* favorable se trouvent dans les cancers du *sein* ou de l ovaire de longue durée *et dans* les cas d épanchement hémorragique

eight for from 4 to 6 months, eighteen for from 6 to 12 months, while three survived for more than a year Thirteen patients were still alive at the time when analysis was closed

Fifteen cases received intracavitary treatment with ^{90}Y or ^{198}Au before or after intracavitary thiotepa therapy A favourable effect of isotope therapy after thiotepa was noted in six out of eleven cases and in three out of four cases a similar effect of isotope therapy prior to thiotepa was observed All the four cases that received thiotepa after isotope therapy belonged to the group of unassessable cases

Discussion

Intracavitary application of cytostatics makes it possible to obtain direct contact with malignant cells and thus to obtain a higher concentration than in systemic treatment THOM (1964) found for instance that in malignant effusions treated with intracavitary thiotepa increasing oedema of the tumour cells occurred within in a few hours After 24 hours, there were signs of necrobiotic changes, with loss of nucleoli, in most of the tumour cells

Our results with thiotepa do not appear to be as satisfactory as those obtained by other workers with alkylating agents (Table 6) However, if the unassessable cases are excluded, and the influence of other simultaneous treatments is disregarded, they are on a level with previous results, although the authors cited do not seem to have excluded their unassessable cases It is possible that our criteria of a positive therapeutic result have been stricter, since the data of assessment are not always accurately defined in other materials It could also be that in the present series the doses of thiotepa were too low, or that too few instillations were employed However, the doses were of such a magnitude that in 61 per cent of the controlled cases they induced mild bone marrow depression A favourable response, if any, appears moreover to be obtained after at the most two instillations As compared with other materials, the series also does not seem to contain a preponderance of cases with carcinoma in sites that usually fail to respond favourably to intracavitary cytotoxic therapy In other words, the results suggest that the effect of intracavitary thiotepa in malignant effusions is not as good as previously assumed

It is always difficult to evaluate the effect of other treatments given at the same time, but assuming they be of less importance compared with intracavitary thiotepa treatment, the results indicate the greatest effect in the groups of mammary and ovarian carcinoma (Table 3) This is in accordance with the findings of WEISBERGER et coll (1955) using HN2, GOODMAN et coll (1965) with KC 33, and BONTE et coll (1956) with ^{198}Au

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Treatment of malignant effusions with intracavitary thiotepa is of indubitable value in quite a large proportion of cases It is devoid of risk to the patients as well as to the staff and entails so little discomfort and so few side effects that its selection for the first therapeutic attempt appears reasonable The treatment seems to be most effective in mammary or ovarian carcinoma of long duration, and in cases of haemorrhagic effusions Pleural effusions appear to react better than peritoneal effusions If the case does not respond by a reduction in the effusion after two instillations of thiotepa, other methods should be tried

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ZUSAMMENFASSUNG

Thiotepa Injektionen in die Pleurahöhle und die Peritonaalhöhle wurden in 86 Fällen durchgeführt Eine günstige Wirkung der Behandlung wurde in 37 Prozent der Fälle erzielt und wenn man zweifelhafte Fälle ausschliesst in 57 6 Prozent. Die beste Voraussetzung für einen guten Erfolg erboten Fälle von andauernden Brust und Ovarial Karzinomen und Fälle mit hämorrhagischen Ergussen

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INTERCOMPARISON OF ABSORBED DOSE IN COBALT 60 TELETHERAPY USING MAILED LiF DOSIMETERS

by

P M PFALZNER and S MALO ALVAREZ

The International Atomic Energy Agency has long been aware of the need for improved dosimetric accuracy in the medical applications of radiation such as in teleradiotherapy Of all radiotherapy centres in the world probably less than 50 % have ready access to standardizing dosimetry laboratories and even these laboratories at present provide only standards of radiation exposure (in roentgen) whereas the decisive quantity in radiotherapy is the absorbed dose (in rad) received by the tissues being irradiated

In order to assist radiotherapy centres particularly in the developing countries with the determination of absorbed dose in ^{60}Co teletherapy the IAEA has set up a postal dose intercomparison service utilizing thermoluminescent LiF powder Prior to putting this scheme into practice the intercomparison procedures were tested with the co-operation of 19 radiotherapy centres in 6 countries The participating institutes are listed in Table 1

This report gives a brief description of the procedures and of the results without identifying the results with any particular institute

Method Each participant was provided with a plastic water tank in which the irradiation was to take place as well as with instructions for the experimental

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Table 2

Intercomparison results

Institute number	Irradiated control capsules*			Test capsules		
	Individual values in per cent of overall mean			Extreme difference	R m s deviation	Difference from mean
20	100 1	101 2	100 7	5 8	1 7	−2 0
21	101 5	100 0	99 3	5 0	1 8	−7 4
22	99 6	98 5	101 1	4 9	1 5	+2 1
24	99 7	98 2	100 1	5 9	2 4	−0 6
25	93 5	—	—	2 8	1 0	−8 3
26	98 7	101 0	100 7	7 0	2 0	−2 3
27	100 6	96 3	101 3	(11 6)	(3 8)	(+2 8)
27				8 6	2 4	+1 8
28	100 8	102 8	99 7	2 8	1 0	+1 0
29	98 9	99 6	100 5	(7 0)	(2 3)	(−8 4)
29				7 0	2 3	+0 4
30	100 4	97 9	99 6	9 9	1 0	+4 2
30	99 6	—	—	5 1	1 6	+3 5
31	101 1	98 1	—	4 4	1 0	+4 0
32	100 2	—	99 8	6 4	2 0	−1 1
33	99 8	101 8	99 4	5 6	1 7	−2 2
34	100 5	97 4	100 5	5 3	1 7	+1 1
35	100 8	—	—	9 9	3 2	0 0
36	97 4	—	—	5 2	1 5	−2 3
37	100 5	102 8	99 6	(7 2)	(2 3)	(+7 0)
37				7 2	2 3	+6 0
38	100 5	101 8	96 7	6 6	2 0	+1 5
A †	100 8	98 5	101 4			
B	99 6	98 9	99 7			
C	98 5	101 1	101 0			

R m s deviation = 1 4 — Average r m s deviation = 1 9

* The unirradiated control capsules in all cases gave readings which were less than 1 % of those of the irradiated test capsules

† A, B and C refer to irradiated control capsules kept in Vienna and read at different dates

in stored luminescence due to unknown heating of the capsules while in transit and (3) to give an indication of the reproducibility of the procedure The unirradiated control capsules served to detect any radiation which the set might have received while in transit

Table 1

Participating institutes

Royal Adelaide Hospital, Adelaide	Australia
The Ontario Cancer Treatment and Research Foundation Ottawa	Canada
The Ontario Cancer Institute Toronto	Canada
Manitoba Cancer Treatment and Research Foundation Winnipeg	Canada
Institut Gustave Roussy Villejuif	France
Radiofysiska Institutionen Lund	Sweden
Regionsjukhuset Örebro	Sweden
Karolinska Sjukhuset Stockholm	Sweden
The General Infirmary Leeds	UK
The London Hospital and Research Laboratories London	UK
Westminster Hospital London	UK
Christie Hospital and Holt Radium Institute Manchester	UK
Regional Medical Physics Department Sheffield	*UK*
Royal Marsden Hospital Sutton Surrey	UK
Lovelace Clinic Albuquerque New Mexico	USA
Argonne Cancer Research Hospital Chicago Illinois	USA
M D Anderson Hospital and Tumor Institute Houston Texas	USA
Memorial Hospital New York N Y	USA
Temple University Hospital Philadelphia Pennsylvania	USA

procedure to be followed —The thermoluminescence readings of all capsules were carried out at the IAEA in Vienna using a commercial TLD read out instrument Some of the precautions taken were (a) before each reading a radioactive phosphorescent light standard was introduced allowing corrections to be made for variations in instrumental sensitivity, (b) the photomultiplier voltage was kept constant at all times, (c) new heating planchets were used after each 15th heating cycle —At approximately monthly intervals, each one of the institutes received and returned one set of LiF capsules (up to a total of 5 sets), each set consisting of two control capsules and three test capsules Each capsule contained some 150 mg of type 7 LiF powder (CAMERON et coll 1964) Each participant was instructed to irradiate the test capsules of each set, one at a time with a cobalt 60 beam of 10 cm×10 cm field size The absorbed dose delivered to the capsules was to be 500 rad at a depth of 5 cm in water, the participant following his own method of dosimetry exactly as if treating a patient One control capsule of each set was irradiated at the IAEA to a fixed dose before mailing, the other control capsule remaining unirradiated Additional irradiated control capsules were retained in Vienna

The irradiated control capsules served three purposes (1) to obtain a decay curve of the stored luminescence as a function of time (2) to detect any decrease

120 days later A root mean square deviation of ±1 4 % was found for the 56 control capsules

The last three columns of Table 2 give the results for the test capsules The fifth column gives the difference between the highest and lowest values as a percentage of the institute s mean, the next column gives the r m s deviation from the institute s mean, and the last column gives the percentage difference between the mean for each institute and the overall mean

Three institutes (Nos 27 29 and 37) when returning the questionnaire but without any knowledge of the final results indicated that they wished to change the dose values they had previously reported These institutes have been listed in duplicate with a prime indicating the revised calculations

Discussion

In Tables 3 and 4, use is made of the data given in the participants completed questionnaires The four methods used by participants to calculate the absorbed dose in water are shown in Table 3 Two of these methods are based on in air *measurements and the* two others on in water measurements for each of these there is again a choice between making the measurement at the actual position of the LiF capsule or at some other point

It will be noted that in all of these methods, both the *cap displacement factor* C_D and the roentgen to-rad factor *f* occur The factor C_D is required to allow for changes in absorption and scatter whenever an ionization chamber *calibrated* to read exposure in an extended air medium is used for measurements in a different medium The participants *reported* values of this factor for water are 0 985 *for the* Baldwin Farmer substandard chamber and the Victoreen 25 R and 100 R *chambers* 0 975 for the Victrometer 250 R chamber, and 0 98 *for the Baldwin Ionex*

The use of the factor C_D *in methods 3* and 4 depends on the definition of TAR (and BSF) The *definition given in ICRU* Report 10d (1963) *is* in terms of ratios of absorbed dose and leads to values for both TAR and BSF slightly differing from the earlier ones (CUNNINGHAM et coll 1965 GUPTA et coll 1966) The use of these values requires a knowledge *of the* cap displacement factor C_D — It appears possible *to formulate* a definition of TAR (*and* hence BSF) such that the factor C_D does not occur explicitly *in* the use of methods 3 and 4 this would be desirable for purposes of practical dosimetry

Table 4 lists all participating institutes and gives the factors employed by them in calculating absorbed dose *from* measured *exposure* values The differences from the overall mean (given in Table 2) *are shown* in column 2 It is instructive to see how much of this difference is due *to* differences in the factors used by

Table 3

Method number	Number of institutes using method	Formulas for calculation of absorbed dose rate from measured exposure rate
1	5	$_WF \times f \times C_D$
2	2	$_WF_{0.5} \times \%DD \times f \times C_D$
3	6	$_AF \times TAR \times f \times C_D$
4	5	$_AF_{0.5} \times BSF \times \%DD \times f \times C_D$

(One participant did not give any information)

Legend
$_WF$ = exposure rate measured in water at position of LiF capsule
$_WF_{0.5}$ = exposure rate measured in water at (SSD + 0.5) cm
$_AF$ = exposure rate measured in air at position of LiF capsule
$_AF_{0.5}$ = exposure rate measured in air at (SSD + 0.5) cm
$\%DD$ = central axis percent depth dose
TAR = tissue air ratio
BSF = backscatter factor
f = roentgen to rad factor (rad/R)
C_D = cap displacement factor
SSD = source to surface distance

Re method 2: One institute used this incorrectly: the exposure rate was measured at the water surface and no correction factor was applied for the required change in distance to 0.5 cm below the surface.
Re method 4: Two institutes used this incorrectly: the exposure rate was measured in air at the SSD instead of at (SSD + 0.5) cm and no correction factor was applied.

At the completion of the series, a questionnaire was sent to each participant concerning the data used by him in determining the administered dose.

Results

Table 2 shows the results obtained with the LiF powder measurements. (Each capsule gave three thermoluminescence readings, the average of which is the measured value for one capsule.) The institute numbers shown are those assigned during the intercomparison (there is no relationship between the order of listing of the institutes in Table 1 and that in Table 2). The left half of Table 2 gives the results obtained with the irradiated control capsules, in percentage of the mean of all the irradiated control capsules. A fading of 5.5 % in the interval from 10 days to 100 days after irradiation was observed, the figures shown here have been normalized to a value at 50 days. All capsules were read after a minimum of 9 days following irradiation, though some readings occurred as much as

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Table 3

Method number	Number of institutes using method	Formulas for calculation of absorbed dose rate from measured exposure rate
1	5	$_{H}E \times f \times C_D$
2	2	$_{H}E_{0.5} \times \%DD \times f \times C_D$
3	6	$_{A}E \times TAR \times f \times C_D$
4	5	$_{A}E_{0.5} \times BSF \times \% DD \times f \times C_D$

(One participant did not give any information)

Legend

$_{H}E$ = exposure rate measured in water at position of LiF capsule
$_{H}E_{0.5}$ = exposure rate measured in water at (SSD + 0 5) cm
$_{A}E$ = exposure rate measured in air at position of LiF capsule
$_{A}E_{0.5}$ = exposure rate measured in air at (SSD + 0 5) cm
$\%DD$ = central axis percent depth dose
TAR = tissue air ratio
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The last three columns of Table 2 give the results for the test capsules The fifth column gives the difference between the highest and lowest values as a percentage of the institute s mean the next column gives the r m s deviation from the institute s mean, and the last column gives the percentage difference between the mean for each institute and the overall mean

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Table 3

Method number	Number of institutes using method	Formulas for calculation of absorbed dose rate from measured exposure rate
1	5	$_WE \times f \times C_D$
2	2	$_WE_{0.5} \times \%DD \times f \times C_D$
3	6	$_AE \times TAR \times f \times C_D$
4	5	$_AE_{0.5} \times BSF \times \%DD \times f \times C_D$

(One participant did not give any information)

Legend

$_WE$ = exposure rate measured in water at position of LiF capsule
$_WE_{0.5}$ = exposure rate measured in water at (SSD + 0.5) cm
$_AE$ = exposure rate measured in air at position of LiF capsule
$_AE_{0.5}$ = exposure rate measured in air at (SSD + 0.5) cm
$\%DD$ = central axis percent depth dose
TAR = tissue air ratio
BSF = backscatter factor
f = roentgen-to-rad factor (rad/R)
C_D = cap displacement factor
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Table 4

	Institute number	Difference from mean %	Recalculated* difference from mean %	Factors used by participants to f rad/R	Factors used by participants to C_λ**
UK	20	— 2 0	Not recalc	—	0 944
UK	21	— 7 4	— 4 2 (— 2 7)	0 974	—
UK	22	+ 2 1	+ 0 7	0 975	—
UK	24	— 0 6	Not recalc	—	0 944
UK	25	— 8 3	(		No information
UK	26	— 2 3	Not recalc	—	0 940
USA	27	+ 1 8	+ 1 4	0 957	—
USA	28	+ 1 0	+ 0 9 (+ 2 4)	0 964	—
USA	29	+ 0 4	— 0 6 (+ 0 9)	0 974	—
USA	30	+ 4 2	+ 2 9 (+ 4 4)	0 965	—
USA	39	+ 3 5	+ 5 1 (+ 6 6)	0 97	—
	31	+ 4 0	No change	0 965	—
	32	— 1 1	Not recalc	—	0 97****
	33	— 2 2	No change (— 0 7)	0 965	—
	34	+ 1 1	+ 2 3 (+ 3 8)	0 965	—
	35	0 0	No change	0 965	—
	36	— 2 3	— 4 2 (— 2 7)	0 96	—
	37	+ 6 0	+ 5 9	0 965	—
	38	+ 1 5	Not recalc	—	0 945

* For the calculations in this column values were taken to be f (water) = 0 965 BSF = 1 035 $\%DD_{80}$ = 78 5 TAR = 0 905 other factors were left unchanged

** $C_\lambda = C_D \times f$ (see ref 2)

participants to calculate absorbed doses If we normalize all results by adopting uniform values for the f factor, BSF, % DD and TAR (as noted in Table 4) we can calculate the resulting percentage changes in the reported doses, and hence obtain revised values for the differences from the mean, as shown in column 3 of the table For three institutes the missing inverse-square law factors were included in the recalculation When account is taken of the need to include also the cap displacement factor C_D in the recalculation, the final revised values for the differences from the mean are as shown in brackets

Table 4 *(cont)*

calculate absorbed doses				
Field size 10 cm × 10 cm			C_D	Method number
BSF	At 5 cm depth			
	DD_{SSD}	TAR		
—	—	—	—	1
1 016 **	58 $0_{50\,2}$***	—	1 0	4
1 030	77 0_{80} ***	—	0 97₅	4
—	—		—	1
a ailable			)	
—	—	—	—	1
1 0?6	79 5_{80}	—	0 98₅	4
—	—	0 90₅	1 0	3
—		0 888	1 0	3
—	—	0 893	1 0	3
1 0?6	74 0_{50}	—	1 0	4
—	—	0 90₅	0 98	3
—	—	—	—	1
—	78 0_{75}	—	1 0	2
—	78 5_{80}	—	1 0	2
1 03₅	78 5_{80}	—	0 98₅	4
—	—	0 893	1 0	3
—	—	0 904	0 98₅	3
—	—	—	—	1

Report d as measured values for a 10 × 8 cm field (n recalculation BSF wa taken as 1 033)

* * Report d as measured values

Conclusions

The results of the intercomparison and the analysis permit certain conclusions to be drawn with respect to the differences between the participating institutes in both the determination of exposure and of absorbed dose

Table 2 (column 7) shows that maximum differences of up to 15 % in absorbed dose to patients may exist between some of the institutes It is seen that four institutes account for the greatest deviations from the mean However two of these reported corrections to their figures resulting in improved values and hence only three institutes deviate by more than 5 % from the overall mean

The recalculated values of Table 4 (column 3), resulting from the adoption of common values for the factors and corrections for cap displacement and inverse square law (where necessary) in the calculation of absorbed dose from the participants exposure measurements, give an indication of the differences in exposure determination between the institutes (values for institutes using method *1 were not recalculated*) The maximum differences (ignoring institute No 25) are seen to be 9 3 %, i e the agreement as regards exposure is better than for absorbed dose but is nevertheless greater than one might expect for well established radiotherapy centres

From the values of the recalculated percent differences, it can be deduced *that the mean of these values is 1 1 % higher than the original overall mean* Taking this into account, it is found that only one institute shows a deviation of more than 5 %, and that the worst deviations are respectively +5 5 % and —3 8 % from the new overall mean It is notable also that all of the six UK participants show a negative deviation from this new mean, and that of the 5 USA participants, four show positive deviations with only one having a small negative value

The reliability of this particular method of intercomparison has proved to be adequate for present purposes as can be seen from Table 2 An indication of the value of this procedure can be obtained by comparing the results for institutes Nos 27, 29 and 37 (as originally stated) with 27′, 29′, and 37′ (as later corrected) in each of the three cases the change leads to improvement in the results

The reliability of the system is indicated by the r m s deviation of ±1 4 % found for all the 56 irradiated control capsules taken together The average of the r m s deviations computed for each institute separately is ±1 8 %—only lightly larger than that of *the irradiated controls—indicating that on the whole* the institutes are self consistent A few institutes, however, do not show such good consistency numbers 30 and 35, for example, both show extreme differences from the mean of 10 %

The handling and mailing procedures of the capsules proved to be simple and nearly trouble free

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SUMMARY

A procedure established by the IAEA for absorbed dose intercomparison in cobalt 60 teletherapy was tested with the cooperation of 19 radiotherapy centres in 6 countries A series of dosimeter capsules containing LiF powder were distributed by mail and after irradiation to an absorbed dose of 500 rad at a depth of 5 cm in water were returned to the IAEA for read-out and evaluation The results permit conclusions to be drawn concerning the reliability of the method of intercomparison and provide an indication of the consistency and range of disagreement existing in both absorbed-dose determination and exposure calibration Root mean square deviations of respectively ±1 4 % and ±1 8 % were found for the readings of irradiated control capsules and test capsules The maximum differences between institutes in absorbed dose and exposure determination were respectively 15 % and 9 %

ZUSAMMENFASSUNG

Ein von der IAEA fur Cobalt 60 Teletherapie ausgearbeitetes Verfahren zur Vergleichung von Energiedosis-Bestimmungen wurde in Zusammenarbeit mit 19 Radiotherapie Zentren in 6 Landern untersucht Zu diesem Zweck wurden eine Reihe von mit LiF Pulver gefullten Dosismeterkapseln per Post an die 19 Institute versandt Nach Bestrahlung mit einer Energiedosis von 500 rad in einer Tiefe von 5 cm Wasser wurden die Kapseln zur Auswertung an die IAEA retourniert Schlussfolgerungen betreffs der Zuverlassigkeit dieser Vergleichsmethode als auch der Konsistenz bzw der Streuung bei der Bestimmung von Energiedosis und Ionendosis werden gezogen Die mittleren quadratischen Fehler bei der Ablesung der bestrahlten Kontrollkapseln bzw Testkapseln betragen ±1 4 % bzw 1 8 % Die Maximal differenzen zwischen den von verschiedenen Instituten ermittelten Energiedosis und Ionendosiswerten betragen 15 % bzw 9 %

RÉSUMÉ

Les auteurs ont mis a l epreuve avec la cooperation de 19 centres de radiotherapie de 6 pays un processus d intercomparaison des doses absorbées en télécobalttherapie processus établi par l AIEA Ils ont envoyé par la poste une serie de capsules dosimetriques contenant de la poudre de LiF qui apres irradiation a une dose absorbee de 500 rad a une profondeur de 5 cm dans l eau ont ete renvoyees a l AIEA pour comptage Les résultats permettent de tirer des conclusions concernant la fidelite de cette méthode d intercomparaison et donnent une indication sur la constance et l importance de la discordance quant à la determination de la dose ab orbée et de l exposition On a trouvé des ecarts standard de respectivement ±1 4 % et ±1 8 % dans la lecture des capsules irradiées temoine et des capsules en expérimentation Les différences maximales entre les divers instituts dans la determination de la do e absorbée et de l exposition ont éte respectivement de 15 % et de 9 %

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2 CODE OF PRACTICE FOR THE DOSIMETRY OF 2 to 8 MV X ray and caesium 137 and cobalt-60 γ ray beams The Hospital Physicists Association Phys Med Biol 9 (1964) 457

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INSTITUT GUSTAVE ROUSSY, VILLEJUIF FRANCE, ET INSTITUT DU CANCER LOUVAIN, BELGIQUE

ETUDE DE LA REPARTITION DES DOSES AUTOUR DE SOURCES PONCTUELLES ALIGNEES

Application en curietherapie gynecologique

par

A. DUTREIX et A. WAMBERSIE

Le remplacement progressif du radium par d'autres radioeléments a permis de renover les techniques d'application des sources radioactives et notamment de développer les méthodes de préparation inactive.

Simultanement et pour faciliter l'utilisation de ces techniques, on a mis au point des sources de forme et de dimensions tres differentes. Ainsi certains auteurs (CARDIS 1968, C. E. A. 1966) proposent des sources de cesium 137 sous formes de petites spheres ou de grains qui peuvent etre assimiles a des points et que nous appellerons par convention "sources ponctuelles".

Les radiothérapeutes, avant d'utiliser ces sources dans des applications pour lesquelles ils ont une grande expérience du radium, désirent savoir à quelles modifications ils peuvent s'attendre dans la repartition des doses. Ceci est particulierement vrai dans le cas des applications gynecologiques pour lesquelles les techniques utilisant les tubes de radium sont bien codifiees et donnent d'excellents résultats cliniques.

Nous avons entrepris l'etude de la répartition des doses dans ce cas mais la plupart de nos conclusions sont valables pour d'autres applications.

Soumis à la Rédaction 13 Mai 1968

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INSTITUT GUSTAVE ROUSSY VILLEJUIF FRANCE, ET INSTITUT DU CANCER, LOUVAIN,
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Le remplacement progressif du radium par d autres radioeléments a permis de renover les techniques d application des sources radioactives et notamment de developper les méthodes de préparation inactive

Simultanement et pour faciliter l utilisation de ces techniques on a mis au point des sources de forme et de dimensions tres differentes Ainsi certains auteurs (Cardis 1968 C E A 1966) proposent des sources de cesium 137 sous formes de petites spheres ou de grains qui peuvent etre assimiles a des points et que nous appellerons par convention 'sources ponctuelles

Les radiotherapeutes avant d utiliser ces sources dans des applications pour lesquelles ils ont une grande expérience du radium désirent savoir à quelles modifications ils peuvent s attendre dans la repartition des doses Ceci est particulierement vrai dans le cas des applications gynecologiques pour lesquelles les techniques utilisant les tubes de radium sont bien codifiees et donnent d excellents résultats cliniques

Nous avons entrepris l etude de la répartition des doses dans ce cas mais la plupart de nos conclusions sont valables pour d autres applications

Soumis à la Rédaction 13 Mai 1968

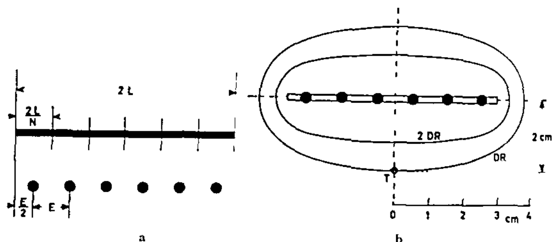


Fig 1 Comparaison de sources ponctuelles alignées et d une source rectiligne continue a) Disposition des sources ponctuelles équivalente à la source continue b) La dose de référence *DR* est définie au point T

Le calcul de la dose par les méthodes manuelles est extremement long et fastidieux et rend difficile toute étude systématique mais nous disposions pour ce travail d'un programme de calcul sur ordinateur (DUTREIX 1967) (Nous tenons a remercier le Centre de Calcul de l Université de Louvain qui a fort obligeamment mis à notre disposition son calculateur (IBM 360—40) *pour cette étude*)

Dans une première partie, nous avons recherché la disposition des sources ponctuelles qui permet d obtenir une repartition des doses aussi semblable que possible a celle correspondant a une source continue, cela pour repondre a la demande de certains curiethérapeutes

Nous avons toutefois négligé pour cette comparaison l autoabsorption dans la source continue, en considerant que la diminution de dose qu elle entraine a l extremité des sources n'est jamais souhaitable et qu il serait donc illogique de chercher à la reproduire avec un autre dispositif

Dans une deuxième partie nous avons cherché à établir des règles simples permettant de calculer la valeur de la dose en un point de référence et de prévoir les dimensions des isodoses en fonction du nombre de sources et de leur disposition

Nous avons enfin étudié l'influence sur la forme des courbes isodoses d un espacement *irrégulier des sources*

I Equivalence entre une source rectiligne continue et des sources ponctuelles

Il est évident que la repartition de la dose autour de sources ponctuelles alignees est d autant plus semblable à celle autour d une source continue

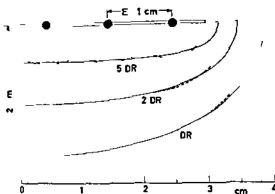


Fig 2 Distribution comparée des doses autour d une source rectiligne continue de 6 cm de longueur radioactive et de 6 sources ponctuelles alignees espacées de 1 cm

que l espacement entre les sources est plus faible (c est à-dire le nombre de sources ponctuelles plus elevé) et que la distance a l axe de ces sources est plus grande

Considerons (Fig 1) une source radioactive rectiligne continue de longueur active $2L$ cm et d activite Q mCi que l on decompose en N élements egaux de longueurs $2L/N$ On peut remplacer chacun de ces N élements par une source ponctuelle placee en son centre et d activite Q/N mCi les N sources ponctuelles sont ainsi regulièrement réparties et l espacement E entre deux sources est egal a $2L/N$

Nous avons fait varier cet espacement entre les sources de 0 5 à 2 cm Pour des espacements inferieurs a 0 5 cm il est difficile de mettre en evidence des differences de repartition des doses meme a quelques millimetres de l axe des sources pour des espacements superieurs a 2 cm les variations de doses meme à grande distance de l axe deviennent trop importantes

Pour inclure largement dans cette etude tous les types de sondes utilises en gynécologie nous avons délibérement fait varier les longueurs actives au delà des limites usuelles et le calcul a ete effectué pour des sources de longueur active variant de 4 a 12 cm

Toutes les doses ont ete estimées en fonction de la dose DR en un point de référence Ce point de réference T est situe dans le plan perpendiculaire a l axe de la source en son centre et à 2 cm de cet axe

Le volume traite est le volume de tissu limité par l isodose dont la valeur est égale à celle de la dose DR au point T

Le volume de surdosage (2 DR) est le volume de tissu limité par l isodose dont la valeur est egale a 2 fois celle de la dose DR au point T De meme on peut également definir des volumes de surdosage 3 DR 4 DR etc

Par convention on appelle

Longueur d'un volume, la dimension de ce volume mesurée dans la direction de l'axe de la sonde,

Rayon de ce volume, le rayon de l'isodose circulaire mesure dans un plan perpendiculaire a l'axe de la sonde a une distance définie du centre de la sonde

L'analyse des résultats des calculs effectués pour les differentes longueurs actives et pour les differents espacements entre les sources nous a permis de comparer de façon précise les volumes précédemment définis et d'en tirer les conclusions suivantes (Fig. 2)

1. Volume traité

A. Rayon. Dans tous les cas envisagés dans cette étude, source continue ou sources ponctuelles, on peut admettre que le rayon du volume traité decroit regulierement quand on se deplace du centre de la sonde vers une extrémite

Le calcul montre que le rayon de ce volume à une distance définie du centre est independant de l'espacement entre les sources, tant que cet espacement est inferieur à 2 cm, il est egal au rayon du volume correspondant a une source continue

Le rayon du volume traite depend tres peu de la longueur de la source au centre de la source, il est égal a 2 cm par définition, a une distance $L/2$ du centre, il est égal à 1,9 cm, à une distance $3L/4$ du centre, il est égal a 1,8 cm pour une source de 4 cm de longueur et à 1,7 cm pour une sonde de 12 cm

Quand on passe d'une source continue de 12 cm de longueur a 6 sources ponctuelles espacées de 2 cm, la diminution du rayon n'est que de 1 mm meme à 6 cm du centre, c'est à dire au niveau de l'extrémité de la partie active de la source continue

B. Longueur. La longueur du volume traite est legerement plus petite lorsque l'on passe d'une source continue à des sources ponctuelles. Elle diminue lorsque le nombre de sources diminue. La variation maximale observée est de 5 mm lorsque l'on passe d'une source continue de 12 cm à 6 sources espacees de 2 cm

2. Volume surdose

A. Rayon. Lorsque l'on considere des isodoses plus proches de la sonde (de valeurs 2 *DR*, 3 *DR*, 4 *DR*) la forme de ces courbes peut etre assez differente dans le cas d'une source continue et dans le cas de sources ponctuelles

En effet pour une source continue le rayon du volume surdose decroit constamment du centre vers les extrémites alors que pour des sources ponctuelles il passe par une série de maximums et de minimums qui sont d autant plus accentues que la valeur de l isodose est plus grande et que les sources sont plus espacees

Dans le cas de l isodose 2 *DR*, l amplitude de la variation du rayon du volume surdosé est pratiquement indépendante de l espacement entre les sources

Ainsi pour une source continue de 12 cm de long le rayon décroit de 11 mm a 10 mm lorsque l on s eloigne du centre a 0,75 *L* dans le cas de 6 sources espacées de 2 cm la variation correspondante du rayon est de 12 a 9 mm

De meme si l on compare une source continue de 4 cm et 3 sources espacees de 1 33 cm le rayon varie de 13 a 11 mm dans les deux cas

B Longueur Les variations de la longueur du volume surdose sont tres semblables à celles observees pour la longueur du volume traité

On peut en deduire que malgré les variations de la forme du volume surdose en fonction du nombre de sources, le volume de tissus surdose est pratiquement constant il a meme tendance à decroitre legerement lorsque le nombre de sources diminue

Des conclusions semblables pourraient etre tirees pour le volume surdose 3 *DR*

3 Dose au contact de la sonde

La dose au contact de la sonde a été etudiée pour des diametres de sonde de 4 mm 6 mm et 8 5 mm et pour des longueurs de 4 à 12 cm

Cette dose qui est toujours tres élevee du fait de la faible distance de la source est uniforme tout le long de la sonde dans le cas d une source continue mais presente des maximums et des minimums tres accentues dans le cas de sources ponctuelles

Cependant la dose minimale ne doit pas etre trop faible pour eviter un sous dosage des tissus et la dose maximale ne doit pas etre delivree a un volume trop important a cause des risques de necrose

La dose minimale au contact diminue au contact de la sonde evidemment lorsque le diametre de la sonde augmente mais meme pour une sonde de 8 5 mm de diametre quelle que soit sa longueur et le nombre de sources ponctuelles la dose minimale est au moins egale à 3 fois la dose de reference au point *T*

Tableau 1

Dimensions du volume traité

Nombre de sources	Espacement	Volume traité	
		Longueur[1] calculée	Longueur réelle
4	1	5,5	5,88
4	2	9	9,06
5	0,8	5,6	5,9
5	1	6,5	6,7
5	1,6	9,2	9,22
5	2	11	10,96
6	1	7,5	7,58
6	1,33	9,33	9,32
6	2	13	12,96
8	0,5	5,75	5,98
8	1	9,5	9,46
8	1,5	13,25	13,12
8	2	17	16,84
10	0,8	9,6	9,54
10	1,2	13,4	13,22

[1] Par la formule empirique (1).

Ainsi, si on délivre 5 000 rad en T, la dose à la paroi de la sonde est au minimum égale à 15 000 rad et aucun sous-dosage n'est à craindre.

La dose maximale au contact de la sonde est déterminée davantage par le diamètre de celle-ci que par le nombre de sources. Ainsi pour une source continue de 6 cm, et pour une dose de 5 000 rad en T, la dose au contact de la sonde passe de 34 000 rad pour une sonde de 8,5 mm de diamètre à 71 000 rad pour une sonde de 4 mm de diamètre. Si on remplace la source continue par quatre sources espacées de 1,5 cm, la dose maximale atteint 49 000 rad pour un diamètre de 8,5 mm et 174 000 rad pour un diamètre de 4 mm.

A partir du moment où la limite de tolérance des tissus est dépassée, la valeur de la dose a moins d'importance que la masse de tissus à laquelle cette dose est délivrée. Or, nous venons de voir que les volumes de tissus surdosés étaient très semblables pour les sources continues ou ponctuelles.

Tableau 2

Doses en rad/jour a 2 cm de sources de cesium ponctuelles alignees

n	Espacement cm						
	0	0 5	0 8	1	1 2	1 5	2
1	190 8						
2	381 6	378 7	369 7	361 9	352 8	337 2	306 5
3	572 4	554 4	523 7	500 0	475 0	438 0	388 0
4	763 2	715 9	652 3	613 0	564 9	511 1	426 8
5	954 0	862 0	765 3	698 4	638 2	555 1	461 7
6	1 144 8	992 0	843 8	764 3	681 5	589 1	479 1
7	1 335 6	1 107 4	914 3	814 8	720 2	616 0	498 5
8	1 526 4	1 209 7	972 4	853 6	750 7	633 4	504 4
10	1 908	1 378 7	1 067	910 6	800 2	663 7	517 3
12	2 290	1 513 2	1 124 9	950 6	824 4		
16	3 053	1 697 8	1 207 8	1 007 0	860 8		
20	3 816	1 820 9	1 258 1	1 038 7			

4 Conclusion

Le remplacement des sources continues par des sources ponctuelles n entraine pas de variations importantes dans la repartition des doses a condition que l espacement entre les sources soit inferieur a 2 cm

Ce sont donc des considerations techniques et pratiques qui devront dicter au radiothérapeute le choix du nombre de sources a utiliser

II Choix du nombre de sources ponctuelles, de leur repartition et de leur activite

Le radiothérapeute qui desire utiliser des sources ponctuelles doit prevoir les dimensions du volume traité et calculer le temps d application en fonction du nombre de sources utilisees et de leurs activites

1 Dimensions du volume traité

Comme nous l avons vu le rayon du volume traite est par definition egal a 2 cm

La longueur de ce volume l (en cm) peut etre calculee à partir d une formule empirique

$$l = (N - 1)\,E + \frac{E}{2} + 2 \qquad (1)$$

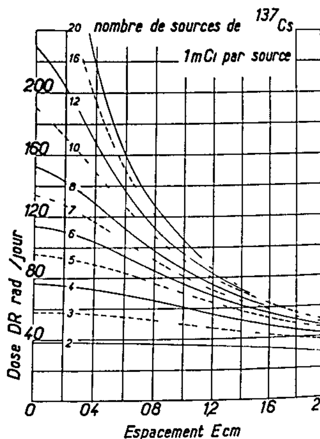


Fig 3 Variation de la dose de référence *DR* au point *T* en fonction du nombre *N* de sources et de leur espacement

ou *E* est l espacement entre 2 sources en cm, c'est a dire que la distance *s* entre une source extreme et l isodose *DR* est égale a 1 cm + *E*/4 L'erreur faite sur cette distance en utilisant cette formule empirique est inferieure a 2 mm comme le montre le Tableau 1

2 Calcul de la dose DR

La dose de reference *DR* delivree a 2 cm de l axe de la sonde dans un plan perpendiculaire en son centre est proportionnelle a l activite des sources et au temps d application , elle n est pas une fonction simple du nombre de sources et de leur espacement C est pourquoi nous avons construit une abaque permettant d évaluer *DR* en rad/jour pour des sources de 1 mCi (Fig 3 et Tableau 2)

A partir de la, la dose totale *DA* delivrée au point de reference *T* au cours d une application se calcule par la formule $DA = DR \quad Q \quad t$ ou Q est l'activité de chaque source en mCi et t le temps d application en jours

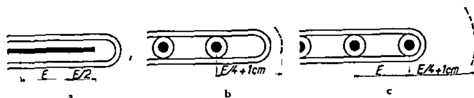


Fig 4 Choix de la disposition des sources dans une sonde intra utérine de longueur donnée a) La partie active de la source continue de radium n atteint pas l extrémite de la sonde la courbe pointillee represente l extremité de l isodose DR b) Une distribution des doses analogue est obtenue en plaçant les sources ponctuelles suivant le schéma défini fig 1 c) La longueur du volume traité peut être augmentee en placant une source ponctuelle à l extrémité de la sonde

3 Choix du nombre de sources et de leur espacement

La longueur S de la sonde est déterminée par la configuration anatomique de la malade mais le radiotherapeute a le choix du nombre de sources et de leur disposition

A S il desire reproduire le plus exactement possible le schema d irradiation obtenu avec une source continue de radium de longueur active $2L$ et d activité Q_{Ra} le nombre N de sources ponctuelles de césium leur espacement E et leurs activités individuelles Q_c sont liees par les relations

$$N \quad E = 2L \quad N \quad \Gamma_c \quad Q_c = \Gamma_{Ra} \quad Q_{Ra}$$

$$\text{d ou} \quad Q_c = 2\ 5 \quad Q_{Ra}/N$$

Γ_c et Γ_{Ra} sont les constantes spécifiques d exposition du cesium et du radium
$\Gamma = 3\ 3$ R cm^2/mCi h
$\Gamma_{Ra} = 8\ 25$ R cm^2/mCi h pour une filtration de 0 5 mm de Pt

Ainsi pour remplacer une source de radium de 30 mCi et de longueur active de 6 cm on peut utiliser 6 sources espacées de 1 cm (Fig 4) les sources ponctuelles extremes etant situees a 5 mm des extremités de la zone active de la source continue La longueur du volume traite est égale a $5 \times 1 + 2 + 0\ 5 = 7\ 5$ cm

L activité de chaque source de cesium devrait etre égale a $(2\ 5 \times 30)/6 = 12\ 5$ mCi pour que les temps d application soient identiques et la dose DR à 2 cm serait egale a $6\ 5 \times 12\ 5$ rad/jour $= 956$ rad/jour

B Le radiothérapeute peut souhaiter profiter de la souplesse d utilisation des sources ponctuelles pour irradier un volume un peu plus long

Il peut dans ce cas placer une source ponctuelle à chaque extrémite de la sonde si la longueur de la sonde est S cm et si l on dispose N sources ponctuelles regulierement espacees de E cm on a $(N - 1)\ E = S$

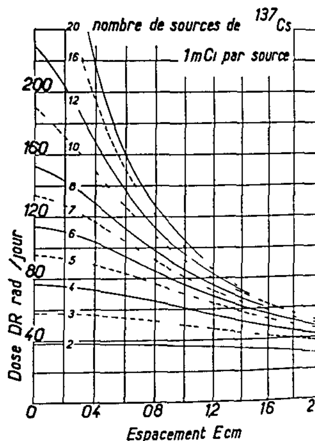


Fig. 3. Variation de la dose de référence *DR* au point *T* en fonction du nombre *N* de sources et de leur espacement.

où *E* est l'espacement entre 2 sources en cm, c'est à dire que la distance *s* entre une source extrême et l'isodose *DR* est égale à 1 cm + *E*/4. L'erreur faite sur cette distance en utilisant cette formule empirique est inférieure à 2 mm comme le montre le Tableau 1.

2. Calcul de la dose DR

La dose de référence *DR* délivrée à 2 cm de l'axe de la sonde dans un plan perpendiculaire en son centre est proportionnelle à l'activité des sources et au temps d'application; elle n'est pas une fonction simple du nombre de sources et de leur espacement. C'est pourquoi nous avons construit une abaque permettant d'évaluer *DR* en rad/jour pour des sources de 1 mCi (Fig. 3 et Tableau 2).

A partir de là, la dose totale *DA* délivrée au point de référence *T* au cours d'une application se calcule par la formule $DA = DR \cdot Q \cdot t$, où *Q* est l'activité de chaque source en mCi et *t* le temps d'application en jours.

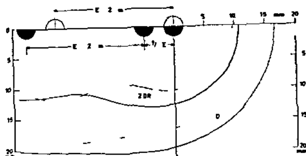


Fig 5 Influence sur le forme des isodoses de l espacement entre les deux sources extrêmes Deux disposit ons des sources ont comparees un espacement regulier (demi cercles blancs et isodoses en point llé) et un espacement reduit entre les deux sources extr mes (demi-ce cles no rs et isodoses en trait cont nu) On a fait co ncider les axes des sondes et les sources extrêmes La reduct on de l espacement entre les sources ext êmes a pour effet d ugmenter le rayon du volume traite au n eau d l ext emité de la sonde a nsi que la distance *s* entre la source extrême et l isodose *DR*

2 Longueur du volume traite

Nous avons etudie les variations de la distance *s* entre la source la plus externe et la limite du volume traite (plus precisement le point d intersection entre l axe de la sonde et l isodose *DR*)

Pour $E = 2$ cm et quand E_d passe de E a $E/4$ *s* augmente de 1 mm pour $\Lambda = 4$ et 5 (*s* passe de 15 a 16 mm) et augmente de 3 mm pour $\Lambda = 7$ et 8 (*s* passe de 14 a 17 mm)

Pour $E = 1$ cm et dans les memes conditions *s* augmente de 2 mm pour $\Lambda = 4$ a 8

Conclusion

L adoption d un espacement non uniforme des sources ponctuelles et en particulier une reduction de E_d ne modifie pas de maniere importante la forme du volume traite dans les limites des dispositions envisagees Le rayon du volume traite au niveau de l extremite de la sonde et la distance *s* peuvent etre augmentees de quelques millimètres (Fig 5)

Toutefois lorsqu on adopte un espacement non uniforme des sources le calcul de la dose de réference au point *T* ne peut pas etre effectue a partir de Fig 3 ou du Tableau 2, il est indispensable de faire le calcul precis correspondant à chaque cas particulier

Ainsi pour une sonde de longueur 6,5 cm, on peut placer 6 sources espacées de 1,3 cm, la longueur du volume traité est égale à $5 \times 1,3 + 2 + 0,65 = 9,15$ cm au lieu de 7,5 cm précédemment. Si on utilise les mêmes sources de 12,5 mCi, la dose à 2 cm est $652 \times 12,5 = 815$ rad/jour.

III. Espacement non uniforme des sources ponctuelles

Compte tenu de la plus grande souplesse dont on dispose avec les sources ponctuelles, on serait tenté d'essayer d'améliorer la forme du volume traité et en particulier d'augmenter son rayon au niveau des extrémités de la sonde et d'allonger la distance entre l'extrémité de la sonde et la limite du volume traité.

Ceci peut se réaliser en concentrant aux extrémités de la sonde une proportion plus grande de radioactivité. L'utilisation de sources d'activités différentes nous paraît peu recommandable en raison du risque possible de confusion entre les sources. Par contre, on peut songer à réduire l'espacement (E_d) entre la dernière et l'avant dernière source, ce qui ne doit pas poser de problèmes pratiques majeurs.

Nous avons étudié de manière systématique l'influence sur la forme du volume traité de la réduction de E_d à une valeur égale à 1/2, 1/3 et 1/4 de l'espacement moyen E. Compte tenu des dimensions des sources que l'on peut être amené à utiliser, il nous paraît difficile de réduire E_d à une valeur inférieure à $E/4$.

1. *Le rayon du volume traité*

Nous avons étudié les variations du rayon du volume traité à la distance $0,75\ L$ du centre de la source et à l'extrémité de celle-ci.

A. Variation du rayon à 0,75 L. Quand on réduit E_d de E à $E/4$ et pour $E = 2$ cm, le rayon du volume traité augmente de 2 mm. Il passe de 18 à 20 mm pour $N = 4$ et 5 et de 19 à 21 mm pour $N = 8$.

Pour $E = 1$ cm et dans les mêmes conditions, le rayon du volume traité augmente de 1 mm, il passe de 18 à 19 mm.

B. Variation du rayon à l'extrémité de la sonde. Quand on réduit E_d de E à $E/4$ et pour $E = 2$ cm, le rayon du volume traité augmente de 2 mm pour $N = 4$ et 5 (il passe de 17 à 19 mm) et augmente de 4 mm pour $N = 6$ à 8 (il passe de 16 à 20 mm).

Pour $E = 1$ cm et dans les mêmes conditions, le rayon augmente de 2 mm.

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DETERMINATION OF TUMOUR DOSE BY TRANSMISSION MEASUREMENTS IN ROENTGEN ROTATION TREATMENT OF THE OESOPHAGUS

by

ULLA BRITA NORDBERG

Determination of the tumour dose in conventional roentgen irradiation is very uncertain because of tissue inhomogeneity especially in the region of the thorax This inhomogeneity is due essentially to the presence of lung tissue the density of which varies from patient to patient as well as within the same patient

Attempts to measure depth doses in lung tissue have been made several times by FAILLA (1921) WEATHERWAX & ROBB (1930), QUIMBY et coll (1934) NAHON & NAIDORF (1952) and DAHL & VIKTERLOF (1955) and others The conditions under which the measurements were made have been very different however and so the results show no great agreement NEUMANN & WACHSMANN (1942) introduced a method for the calculation of the target dose in rotation treatment based on the measurement of transmission in principle on the conception of tissue air ratio (TAR) ROBBINS & MESZAROS (1954) determined the TAR value of homogeneous media of different shapes and sizes by phantom measurements for 250 kV roentgen rotation irradiation LIDEN (1948) described dose determination directly in the oesophagus this method has been employed

From the Department of Radiation Physics (Director Prof K Lidén) the University of Lund Sweden Submitted for publication 1 July 1968

RÉSUMÉ

Pour les applications gynécologiques (sondes intrautérines) le remplacement des sources continues par des sources ponctuelles ne modifie pas de manière importante la distribution des doses à condition d adopter entre les sources un espacement qui ne soit pas supérieur à 2 cm Ceci concerne tant la forme et les dimensions du volume traité que celles des volumes surdosés Des tableaux et des graphiques sont proposés permettant le calcul rapide de la dose de référence et des dimensions du volume traité pour des sources ponctuelles régulièrement espacées La diminution de l espacement entre les sources extrêmes ne modifie pas de manière importante la forme du volume traité mais nécessite un calcul particulier des doses

SUMMARY

The dose distribution in gynecologic treatments (intrauterine applicators) will not be much influenced by the substitution of point sources for continuous sources on condition that the distance between the sources is kept below 2 cm This applies for the shape and dimensions of the treatment volume as well as of volumes receiving overdoses Tables and diagrams are presented for a rapid determination of the reference dose and the dimensions of the treatment volume when using point sources regularly interspaced A reduction of the distance between the extreme sources leads to no important modification of the treatment volume but necessitates a separate dose calculation

ZUSAMMENFASSUNG

Die Dosisverteilung bei gynakologischer Radiotherapie (intrauterine Sonde) wird bei der Substitution kontinuierlicher Strahlungsquellen gegen Punktquellen nicht viel beeinflusst wenn man die Abstande zwischen den Strahlungsquellen unter 2 cm halt Dies ist sowohl fur die Form und die Dimensionen des behandelten Volumens wie fur das uberdosierte Volumen geltend Tabelle und Diagramme werden fur die schnelle Berechnung der Referenzdosis und die Dimensionen des Behandlungsvolumens bei Anwendung von Punktquellen die in gleichen Abstanden placiert sind vorgeschlagen Bei einer Reduktion des Abstandes zwischen den extremen Quellen wird das Behandlungsvolumen nicht viel beeinflusst aber eine besondere Dosisberechnung ist erforderlich

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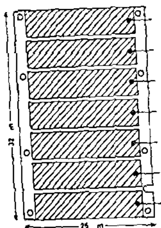


Fig 2 Inner electrode with the seven graphite sections of the transmission chamber

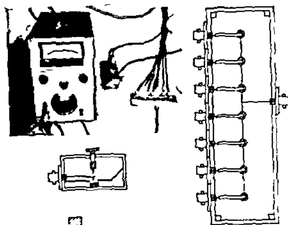


Fig 3 Switch to 7 sectioned transmission chamber The striped areas indicate the insulator

The oesophagus is surrounded by tissue of variable thickness with an average density of 1 g/cm³ Deviations from calculations by the TAR method thus ought to be of somewhat less importance than for a tumour situated in the lung parenchyma However the investigation has shown that this decrease in the dose due to reduced scattering is still quite observable

Mathematical calculations for each treated patient would be time consuming and uncertain Often a relatively long cylinder extending through most of the thorax of the patient and including varying amounts of lung parenchyma is irradiated The heart and the diaphragm may be included in the radiation beam

The aim of this investigation has been to calibrate different transmission values by simultaneous measurements in the oesophagus and in the transmitted beam These calibrations can then be used to calculate the target dose in roentgen rotation treatment of oesophageal tumours and to estimate the variation of the dose in the cranio-caudal direction In this way the unevenness of the dose can be eliminated by means of compensating filters

Transmission (T) is here defined as the ratio between the exposure rate of the primary radiation transmitted *through* a patient measured at some point beyond him and the exposure rate of the primary beam itself at the same *point*

The *treatment technique* includes the following technical data focus-axis distance 60 cm focus-fluoroscopic screen distance 120 cm beam quality 200 kV external filter 0 2 mm copper, which means a first HVL of 0 7 mm Cu The patient is treated in a sitting position with arms raised over his head



Fig 1 Transmission chamber placed on the tube side of the fluoroscopic screen

by GYNNING (1951) O CONNOR (1956) as well as JACOBSSON & KNAUER (1956) have discussed two modifying, mutually counteracting factors reduced attenuation, which increases the dose to the tumour within a region of lower density and reduced scattering, which decreases the dose to the tumour in such a region O CONNOR attempted to estimate the influence of each of these two factors, and he has confirmed his calculations in three patients by measurements with small Sievert chambers, placed directly in the oesophagus JACOBSSON & KNAUER made measurements in a heterogeneous phantom for some special treatment techniques and obtained correction factors due to reduced scattering as well as reduced absorption DICKSON & MORGAN (1961) employed NEUMANN & WACHSMANN'S method of calculation and correlated their calculations with four measurements in patients The measured values were not very accurate but they nevertheless indicated some agreement with the calculations KELLER & ROK (1963) published a collection of tissue factors for different depths in the thorax and abdomen based on measurements of exit exposure DAHL & VIKTERLOF (1960) measured the cranio caudal variation in transmission with several small condenser chambers and then constructed compensating filters to make the target dose homogeneous along the oesophagus

The individual ability of the thorax to absorb and to scatter radiation varies considerably NAHON & NAIDORF indicated that there is a variation of 250 % in exit exposure for comparable regions of the same thorax thickness in patients JACOBSSON & KNAUER indicated that the exit exposure may vary considerably when measured with opposite beam directions Measurements directly in the tumour region are, of course the most reliable ones However, even if the tumour is situated in the oesophagus such measurements are not always possible, in six out of the 50 cases included in the present investigation such measurements could not be made

Calculation of target dose based on water equivalent thickness determined by means of transmission measurements does not take into account the variation in the dose contribution of scattered radiation at the site of tumour With the rotation technique one is for practical reasons limited to measuring the transmission

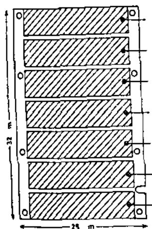


Fig 2 Inner electrode with the seven graphite sections of the transmission chamber

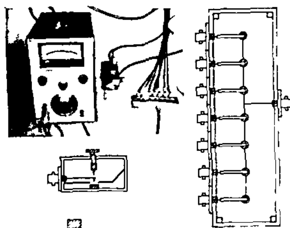


Fig 3 Switch to 7-sectioned transmission chamber The striped areas indicate the insulator

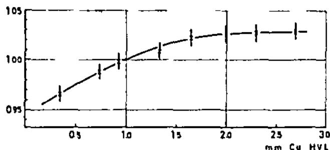
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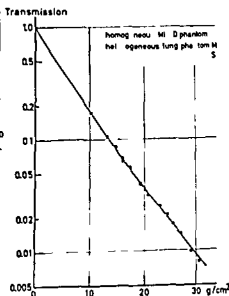


Fig 4 (above) Energy response of the transmission chamber normalized to 1 0 for HVL=1 0 mm Cu Vertical lines indicate the spread for different sections of the chamber

Fig 5 (right) Transmission as a function of phantom thickness in g/cm² for a solid mix D phantom and for two heterogeneous lung phantoms HVL=0 65 mm Cu for the primary radiation

Measuring equipment

The ionization chamber which is used to measure the transmission has an area of 25 cm×32 cm and is placed in contact with the tube side of the fluoroscopic screen (Fig 1) The construction of this chamber has been previously described (NORDBERG 1962) The walls and the central electrode are made up of 2 mm thick perspex sheets The inside walls of the chamber are covered with a thin conducting layer of graphite and serve as the other electrode of the chamber The design of the central electrode is shown in Fig 2 The graphite layer is divided into 7 separate sections, each one having a separate lead through the surrounding metal frame The chamber has a thickness of about 15 mm and is completely roentgen transparent except for the frame The outside walls of the chamber are covered with graphite and grounded The seven leads are joined to a switch situated in the roentgen control room (see Fig 3 for the design of the switch) In the chamber, condensers of 50 000 pF are joined parallel to each section The total capacity of each section and its corresponding cable is about 200 pF An electrometer with a low input capacity (5 pF) is used as measuring instrument A power supply in the control room keeps the inside walls at 300 V and the central electrode is grounded before starting the measurements

The sections of the central electrode are orientated in a vertical row and each section is 4 cm high and 24 cm wide, thus corresponding to an area of 2 cm× 12 cm at the place of the rotation axis The field size at the axis can vary between 4 and 8 cm in width and 10 and 17 cm in height i e along the oesophagus

Table 1

Response per unit field width for different field widths and phantom thicknesses

Field width cm	Equ square area cm	A Measurements without grid Phantom thickness, in cm				B Measurements with parallel grid Phantom thickness in cm			
		10	13	16	19	10	13	16	19
4	37	1 22	0 76	0 46	0 29	0 87	0 53	0 33	0 21
5	50	1 26	0 76	0 47	0 29	0 88	0 54	0 33	0 21
6	64	1 29	0 77	0 48	0 30	9 89	0 54	0 34	0 24
8	9?	1 29	0 79	0 48	0 30	0 89	0 54	0 33	0 21

The irradiated area of each section is directly proportional to the width of the field When short treatment fields are used the outer sections of the chamber will be hit only by the penumbra of the radiation beam The charge that each section accumulates during the treatment of a patient is the measure of the exposure caused by the energy fluence from a horizontal cross-section of the patient approximately 2 cm thick during a certain number of full revolutions a presumption being that scatter contribution from other sections can be neglected

The quality of the primary radiation corresponds to a first half value layer of about 0 7 mm Cu The first half value layer of the transmitted radiation measured in broad beam geometry is between 1 5 and 3 mm Cu depending on the thickness of the patient The response of the chamber (normalized to 1 for the mean value of the response of the sections for a half value layer of 1 mm Cu) is shown in Fig 4 as a function of the quality of the irradiation The energy dependence is negligible within the quality range of interest for all practical purposes the variation in the response between the different sections (indicated by a vertical line in Fig 4) can also be neglected The variation in sensitivity from one section to another is probably due to the slightly varying height of the graphite sections

For the low exposure rate at the place of the chamber less than 2 R/min no loss takes place because of the recombination for a field strength of about 700 V cm For accurate measurement of the transmission the chamber must not be hit by scatter radiation from the patient The ionization chambers usually have a distance of between 40 and 50 cm to the patient After the beam has passed through 10 cm of water the ratio between the fluence of scattered photons leaving the phantom in directions aiming at a given point in the chamber and the fluence of primary photons towards this same point is about 0 06 The variation of the secondary contribution from the smallest to the largest field used is

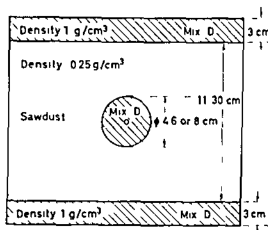


Fig. 6. Cross section of the lung phantom used for the calibration.

within ±30 %. After the beam has passed through 15 cm of water, this ratio is twice as much as for 10 cm. The influence of the variation in area is the same (BJARNGARD & HETTINGER 1961, LEGARE 1964).

If the chamber is hit only by primary radiation the response per unit field width should be constant for different field sizes provided the exposure rate is constant all over the cross section of the roentgen beam. This quotient, determined for 4 different field widths and 4 different thicknesses of a homogeneous mix D phantom, is given in Table 1-A. The values for each size of the phantom lie within ±2 %. This experimental series was repeated with a parallel grid (62 lamellae/inch, ratio 1 : 5.5) in front of the transmission chamber (Table 1-B). In this case the spread is within ±1.5 %. The influence of the grid, measured as the relation between the quotient with grid and the quotient without grid, for all field widths and all phantom sizes, lies within 0.69 and 0.72. This reduction corresponds approximately to the grid attenuation of the primary photons. This variation in sensitivity and grid effect for different areas and phantom sizes is so small that the contribution from scattered photons can be considered negligible.

Determination of the transmission through homogeneous mix D blocks and heterogeneous lung phantoms (mix D, sawdust) of different thicknesses with a beam aperture of 5° (Fig. 5) gives a first half value layer for the primary radiation of about 3.7 cm mix D, corresponding to a mono energetic radiation of about 80 keV. The first half value layer of copper determined with narrow beam geometry and with an ionisation volume of 1 cm³ gives a value of about 70 keV. The sixth half value layer is about 5 cm of mix D. The HVL limit of the primary

beam is 5 1 cm of water Since mix D and water are supposed to have the same linear absorption coefficient, the measurements cited give the actual transmission values Fig 5 also hows that the attenuation curve is the same for a homogeneous absorber when the thickness is measured in g/cm

The transmission chamber is placed directly in contact with the tube side of the fluoroscopic screen which consists of a Pertinex plate (0 4 g cm) causing backscatter radiation to the chamber This contribution has been experimentally determined to be about 9 % for the transmitted beam which is approximately independent of the various radiation parameters employed For the primary quality the contribution is 12 % These values agree with calculations made from published data (QUIMBY & LAURENCE 1940 WACHSMANN & DIMOTSIS 1957) Therefore the backscatter contribution merely necessitates a constant correction factor in the determination of the transmission

The electric charge released during the irradiation is stored in the ection itself the cable and the condenser of the switch The polarization voltage of the chamber is 300 V and the voltage change of a section will never exceed 30 V This gives constant sensitivity during the whole irradiation After irradiation the sections are successively connected with the electrometer by means of the corresponding buttons of the switch The switch is constructed so as to prevent rubbing of the insulators and as a result it does not contribute to the charge

Calibration of transmission

Determination of the TAR values corresponding to different transmission values has been made by measurements with heterogeneous lung phantoms of different constructions and by simultaneous measurements in the patients oesophagi and in the transmitted beam

1 Calibration by means of phantom measurements The design of the lung phantom is shown in Fig 6 It has a central circular mix D cylinder with a measuring channel of about 6 mm diameter This cylinder is surrounded by saw dust compressed to a volume weight of 0 25 g cm³ (DAHL & VIKTERLOF 1960) between two parallel mix D blocks each 3 cm thick The diameter of the mix D cylinder was 4 6 or 8 cm For each diameter the total phantom thickness varied from 17 to 36 cm (The phantoms designated S M and L have diameters of 4 6 and 8 cm respectively) In another series the thickness of the two outer mix D blocks varied from 3 to 11 cm (the phantom being designated by Sa) while the parameters inside the phantom were kept constant Measurements have been made simultaneously with the transmission chamber and with several condenser chambers in the phantom channel The phantom was not rotated The whole series has been repeated for different field widths

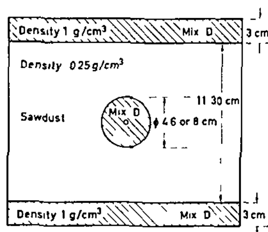


Fig 6 Cross section of the lung phantom used for the calibration

within ±30 % After the beam has passed through 15 cm of water, this ratio is twice as much as for 10 cm The influence of the variation in area is the same (BJARNGARD & HETTINGER 1961, LEGARE 1964)

If the chamber is hit only by primary radiation the response per unit field width should be constant for different field sizes provided the exposure rate is constant all over the cross-section of the roentgen beam This quotient, determined for 4 different field widths and 4 different thicknesses of a homogeneous mix D phantom, is given in Table 1 A The values for each size of the phantom lie within ±2 % This experimental series was repeated with a parallel grid (62 lamellae/inch, ratio 1 5 5) in front of the transmission chamber (Table 1 B) In this case the spread is within ±1 5 % The influence of the grid measured as the relation between the quotient with grid and the quotient without grid, for all field widths and all phantom sizes, lies within 0 69 and 0 72 This reduction corresponds approximately to the grid attenuation of the primary photons This variation in sensitivity and grid effect for different areas and phantom sizes is so small that the contribution from scattered photons can be considered negligible

Determination of the transmission through homogeneous mix D blocks and heterogeneous lung phantoms (mix D, sawdust) of different thicknesses with a beam aperture of 5° (Fig 5) gives a first half value layer for the primary radiation of about 3 7 cm mix D, corresponding to a mono energetic radiation of about 80 keV The first half value layer of copper determined with narrow beam geometry and with an ionisation volume of 1 cm³ gives a value of about 70 keV The sixth half value layer is about 5 cm of mix D The HVL limit of the primary

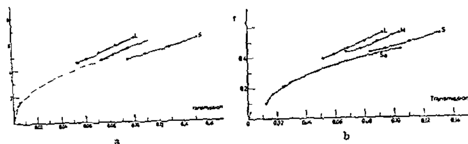


Fig 8 a) The curves indicated by long and short dashes correspond to those in fig 7 calculated for an equivalent square area of 80 cm The full drawn curves illustrate phantom measurements for an equivalent square area of 74 cm L M and S indicate different phantom constructions b) The curves indicated by long and short dashes correspond to those in fig 7 calculated for an equivalent square area of 40 cm The full-drawn curves illustrate phantom measurements for an equivalent square area of 42 cm L, M S and Sa indicate different phantom constructions

oesophagus was determined The condenser chambers are designed for an exposure of about 300 R Their sensitivity as a function of energy is almost constant (±1 %) within the energy interval used The effective energy of the secondary radiation corresponds to a HVL of about 0 3 mm Cu for the actual irradiation conditions (HETTINGER & LIDEN 1960) The scattered radiation irradiates the chamber almost isotropically The chamber has a slight radiation direction dependence which causes an increase of the calibration constants of less than 2 % (LIDEN 1961)

Results and Discussion

The TAR as a function of the transmission is shown in Fig 7 The measurement values correspond to the middle part of the treated region of the patients The values are marked differently for two different intervals of the field size one interval equivalent to a square area of 40 to 60 cm (●) and the other 60 to 80 cm (O) with 19 and 28 points for each interval respectively One patient had a field size smaller than 40 cm (O) and another had a field size larger than 80 cm (×) The full drawn line in Fig 7 is a second degree curve with coefficients calculated from the point lattice by means of the least square method (T=0 44 (TAR) −0 014 TAR) The two curves indicated by short dashes have been drawn with TAR values calculated from the British Journal of Radiology Suppl 10 for field sizes of 40 and 80 cm respectively (ref 5) The relative pread of these two curves for different values of transmission has been transformed to the full drawn curve and is indicated by long dashes on either

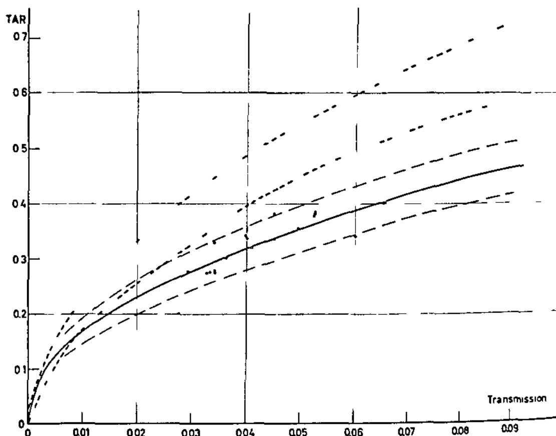


Fig 7 TAR as a function of the transmission indicating patient s measurements field sizes equivalent to square areas of 40 to 60 cm^2 (●) 60 to 80 cm (⊙) > 80 cm (×) < 40 cm (○) The full drawn curve T = 0 44 (TAR)^2—0 014 TAR has been calculated to fit the measurements Curves indicated by short dashes have been calculated for homogeneous material and for equivalent square areas of 10 cm (lowest curve) and 80 cm respectively The curves indicated by long dashes have been calculated to give the same relative spread for field size variation of experimental full drawn curve

2 *Calibration by means of patient measurements* Calibration measurements have been made for all the patients during a continuous period of about 2 years (1960—1962), except in six patients in whom oesophageal measurements could not be made At least three reliable measurement values are recorded for each patient The catheter normally contains 8 small condenser chambers and 3 indicators, permitting localization of the measuring catheter on the fluoroscopic screen Sometimes even a roentgen film has been exposed to check the position of the catheter Only those measuring values have been used where the oscillation of the catheter was small and the measuring points could be localized within ±0 5 cm In this way the dose distribution along the whole treated region of the

sidered valid for 60 cm by correcting for areas different from 60 cm in accordance with already tabulated TAR values Even without this correction 85 % of the measuring points lie within ±7 % of the curve of calibration

The measuring points cover a transmission variation from 0 01 to 0 09 and the weights of patients vary between 35 and 95 kg Attempts to correlate the individual spread in Fig 7 to weight, age sex and localization of the tumour have failed The material is furthermore not large enough to arrive at a significant correlation

A comparison of TAR transmission curves calculated from the Table in ref 5 and from patient measurements for the same size of area clearly shows the loss of dose caused by the reduced contribution of scattered radiation from the thorax compared to the contribution from homogeneous material with a density of 1 g cm³ at the same water equivalent depth

The phantom measurements have been drawn in Fig 8a together with both curves for the maximal area in Fig 7 and in Fig 8b together with corresponding curves for the minimal area The field sizes of the phantom investigations were 74 and 42 cm respectively which measurements approximately correspond with 80 and 40 cm respectively There are three phantom curves in Fig 8a indicated by L M and S corresponding to the diameters of 8 6 and 4 cm of the mix D cylinder These curves were run before and during the same time interval as the calibration with patients was made and therefore the transmission interval later turned out to have been chosen too high Nevertheless it is easily seen that the M and S curves lie nearest to the patient curve while as would be expected the L curve lies nearest the curve of the homogeneous material In Fig 8b another S curve designated Sa is drawn in addition to the L- M and S-curves this new curve corresponds to a series of investigations with a constant amount of lung tissue but with varying thicknesses of the outer mix D blocks (Fig 6) The S curve and the Sa-curve should touch each other for a transmission of about 0 09 however in Fig 8b the curves run at a distance of 4 % of the TAR value This discrepancy can easily be attributed to experimental errors e g repacking of sawdust between the two series

The Sa curve was determined when the actual transmission range was better known and is in agreement with the corresponding patient curve for a transmission of more than 2.5 %

The TAR can be written as follows

TAR =TAR B_p

where a=field size in cm at measuring point P

TAR =TAR of point P with an irradiated area=a cm² at this point

TAR =TAR of point P with an infinitesimal irradiated area

B_p=dose buildup at point P

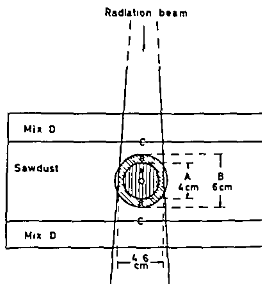


Fig 9 Radiation geometry and different scatter compartments used in the calculation of dose contribution of scattered radiation from different parts around the measuring channel in the phantoms

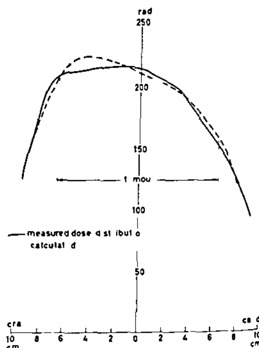


Fig 10 Dose distribution along the oesophagus The full drawn curve is from measurements directly in the oesophagus and the dashed curve has been determined from transmission measurements

side of the full drawn one Between these two curves lie 40 points The total number of points is 47 The two extreme points lie outside this interval As there is some displacement of the means of the values in the interval 40 to 60 cm and 60 to 80 cm" towards smaller and greater TAR, respectively greater accuracy can probably be achieved if the experimental calibration curve is con

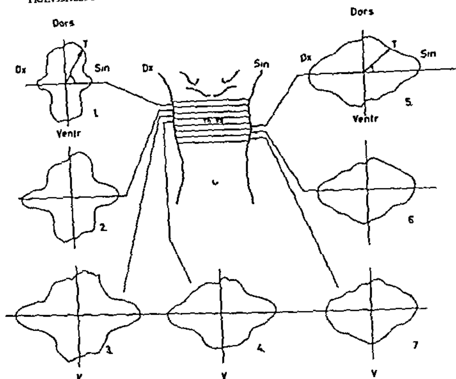


Fig 11 Transmission variations during a full revolution shown as a polar diagram for each of the seven levels of the thorax indicated in the middle of the figure

centimeter thick around the cylinder in (1) $(B_D\text{-}1)_B$ and (3) the remaining irradiated phantom volume $(B_D\text{-}1)_C$

If the contribution from a volume is supposed to be proportional to density and if furthermore the change of filtration of the scattered contribution is neglected homogeneous material will get $(B_D\text{-}1)_A = 0.6$ for 40 and 80 cm $(B_D\text{-}1)_B$ also remains approximately constant 0 3 while $(B_D\text{-}1)_C$ increases from 0 5 to 1 1 in agreement with the corresponding increase of the irradiated volume This means that the dose contribution of scattered photons from a surrounding cylinder with a radius of 2 cm is between 20 and 25 % of the total dose

Dose variation along the oesophagus The relation between the transmission and TAR which has been shown in Fig 7 is only valid in the middle of the irradiated field where B_D is at its maximum This means that a transmission determined for a point outside the field center would not be directly transferred to

Table 2

TAR variation along a field and corresponding variation in dose contribution from scattered radiation for three different transmissions

Distance from the centre of the field (field length 2a)	$\frac{TAR}{TAR_{centre}}$	$\frac{B_D-1}{(B_D-1)_{centre}}$ Transmission (equiv square area 60 cm²) 0 01	0 04	0 09
1 00 a	0 70	0 6	0 4	0 4
0 75 a	0 91	0 9	0 8	0 8
0 50 a	0 97	1 0	0 9	0 9
0 25 a	0 99	1 0	1 0	1 0
0 00 a	1 00	1 0	1 0	1 0

TAR is calculated from The British Journal of Radiology, Suppl 10 (ref 5) In Fig 5, TAR can be derived from the transmission for half the phantom thickness in g/cm², which gives the actual transmission This curve, however, is *not made with a perfect narrow beam geometry and there are no* measuring points in that region of the curve where the interpolation must be done B_D calculated from the patient curve (equivalent square area 60 cm), lies between 2 and 3

TAR_o is calculated to be 0 234 for transmission of 0 085 (from Fig 5 about 0 25)

For a field size of 40 cm²

TAR_S	= 0 430 corresponding to	$(B_D)_S$	= 1 84
TAR_M	= 0 478 «	« $(B_D)_S$	= 2 04
$TAR_{homogeneous}$	= 0 572 «	« $(B_D)_{max}$	= 2 44

For a field size of 80 cm²

TAR_S	= 0 467 corresponding to	$(B_D)_S$	= 2 00
TAR_M	= 0 517 «	« $(B_D)_M$	= 2 21
$TAR_{homogeneous}$	= 0 710 «	« $(B_D)_{max}$	= 3 07

B_D 1 can be expressed (Fig 9) as the sum of the contribution from (1) a cylinder of radius 2 cm around the measuring channel (B_D 1)$_1$, (2) a volume cut out by the geometrical limitation of the radiation beam from a shell one

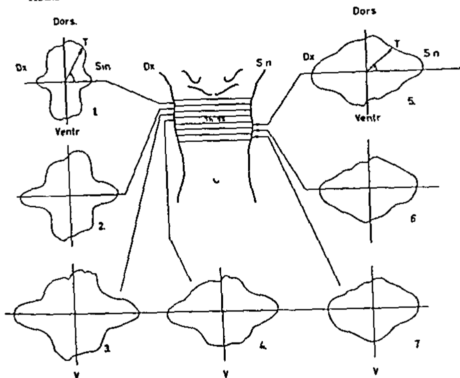


Fig 11 Transmission variations during a full revolution shown as a polar diagram for each of the seven levels of the thorax indicated in the middle of the figure

centimeter thick around the cylinder in (1) $(B_D\text{-}1)_B$ and (3) the remaining irradiated phantom volume $(B_D\text{-}1)_C$

If the contribution from a volume is supposed to be proportional to density and if furthermore the change of filtration of the scattered contribution is neglected homogeneous material will get $(B_D\text{-}1)_A = 0\ 6$ for 40 and 80 cm $(B_D\text{-}1)_B$ also remains approximately constant 0 3 while $(B_D\text{-}1)_C$ increases from 0 5 to 1 1 in agreement with the corresponding increase of the irradiated volume This means that the dose contribution of scattered photons from a surrounding cylinder with a radius of 2 cm is between 20 and 25 % of the total dose

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Distance from the centre of the field (field length 2a)	$\frac{TAR}{TAR_{centre}}$	$\frac{B_D-1}{(B_D-1)_{centre}}$		
		Transmission (equiv. square area 60 cm²)		
		0.01	0.04	0.09
1.00 a	0.70	0.6	0.4	0.4
0.75 a	0.91	0.9	0.8	0.8
0.50 a	0.97	1.0	0.9	0.9
0.25 a	0.99	1.0	1.0	1.0
0.00 a	1.00	1.0	1.0	1.0

TAR is calculated from The British Journal of Radiology, Suppl. 10 (ref. 5). In Fig. 5, TAR can be derived from the transmission for half the phantom thickness in g/cm², which gives the actual transmission. This curve, however, is not made with a perfect narrow beam geometry and there are no measuring points in that region of the curve where the interpolation must be done. B_D calculated from the patient curve (equivalent square area 60 cm²), lies between 2 and 3.

TAR is calculated to be 0.234 for transmission of 0.085 (from Fig. 5 about 0.25).

For a field size of 40 cm²

TAR_S = 0.430 corresponding to $(B_D)_S$ = 1.84
TAR_M = 0.478 « « $(B_D)_M$ = 2.04
$TAR_{homogeneous}$ = 0.572 « « $(B_D)_{max}$ = 2.44

For a field size of 80 cm²

TAR_S = 0.467 corresponding to $(B_D)_S$ = 2.00
TAR_M = 0.517 « « $(B_D)_M$ = 2.21
$TAR_{homogeneous}$ = 0.710 « « $(B_D)_{max}$ = 3.07

$B_D - 1$ can be expressed (Fig. 9) as the sum of the contribution from (1) a cylinder of radius 2 cm around the measuring channel $(B_D - 1)_1$; (2) a volume cut out by the geometrical limitation of the radiation beam from a shell one

Development of the method The charge of a chamber section accumulated during a treatment gives an integrated average of the patient transmission in all beam directions through the oesophagus during a full revolution Fig 11 shows a considerable variation in the differential transmission for different angles but the polar diagrams also illustrate the symmetry of opposite directions The measurements are carried out with a heterogeneous lung phantom built on a real skeleton corresponding recordings have also been made for patients. The calibration of this differential transmission must be made by continuously recording radiation detectors introduced in the oesophagus (BENNER et coll 1959) The average transmission values for different directions through a patient and the transmission of the average thickness of the cross-section in the same directions agree within 7 % for the patients included in the group investigated

The error caused by the integration can therefore be neglected

SUMMARY

A device for simultaneous measurement of the transmission through a patient at different levels is described Correlation between target dose and transmission is obtained by measurements in phantoms as well as in patients The discrepancy in relation to conventional tissue equivalent calculations are discussed

ZUSAMMENFASSUNG

Eine Vorrichtung fur gleichzeitige Transmissionsmessungen in verschiedenen Ebenen eines Patienten wird beschrieben Korrelation zwischen der Herddosis und der Transmission wird durch Messungen in den Phantomen sowie in den Patienten erhalten Die Diskrepanz im Verhaltnis zu den gewohnlichen gewebe aquivalenten Bestimmungen wird diskutiert

RÉSUMÉ

L auteur decrit un dispositif de mesures simultanees a differents niveaux de la transmission du rayonnement à travers le malade au cours de la roentgenthérapie rotatoire des tumeurs de l oesophage Il obtient la correlation entre la dose à la cible et la dose transmise par des mesures sur des fantomes et sur des malades L auteur examine les discordances avec les calculs faits au moyen des équivalents de tissus habituels

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2 BJARNGARD B and HETTINGER G Spectra of scattered radiation behind slabs of water irradiated by X rays Arkiv Fysik 20 (1961) 517

TAR, valid for this point, by using the curves in Fig 7 For a homogeneous phantom the variation of the transit exposure along the field is relatively small and shows only the penumbra of the primary radiation which is independent of field length while the corresponding variation of dose inside the phantom is considerable The influence of the penumbra is here the same as for the transit exposure and is therefore relatively small, but the variation of the scattered contribution is important The TAR variation along the field has been determined for different irradiation geometries and has been found to be very much similar if the distance to the central point is expressed in units of field length (Table 2)

The last columns of Table 2 show the variation of scattered contribution along the field for three different transmissions calculated from corresponding variations of TAR When calculating the dose distribution, the variation of the primary beam intensity must also be considered

If the target doses, thus determined, are correlated with simultaneously measured doses in the oesophagus of different patients, there is very good agreement Fig 10 shows a dose distribution with the accustomed agreement between calculation and measurement in the patient

Target dose The TAR values valid for a homogeneous water equivalent thorax have been calculated from cross sections drawn at different levels of the patients included in this investigation This method results in an underestimation of the target dose, averaging 20 % (extreme values 0 and 40 %) Calculation of the target dose in homogeneous material by means of transmission measurements results, however, in an overestimation of the actual dose by between 20 and 40 %

The measuring and calculation method now described for the determination of the target dose in rotation treatment has been used for about six years

Daily measurements of the transmission along the treatment field constitute a more exact checking of the reproducibility of the treatment than the mere reading of an output monitor in front of the roentgen tube The transmission is very sensitive to density changes in the patient An increase of density corresponding to 1 cm of water gives a decrease in the transmission of between 15 and 18 % The corresponding decrease in the tumour dose is between 7 and 9 %, as calculated from Fig 7 A change in transmission of 10 % corresponds to a change in the target dose of 4 to 5 % There is sometimes a continuous transmission change in a patient during a treatment session This causes a corresponding continuous change of TAR, which change has been verified by direct measurements in the oesophagus of several patients An investigation of these patients from a medical point of view has been performed in order to find some correlation between transmission changes and irradiation effects of different kinds (NORDBERG et coll 1967)

Development of the method The charge of a chamber section, accumulated during a treatment gives an integrated average of the patient transmission in all beam directions through the oesophagus during a full revolution Fig 11 shows a considerable variation in the differential transmission for different angles but the polar diagrams also illustrate the symmetry of opposite directions The measurements are carried out with a heterogeneous lung phantom built on a real skeleton corresponding recordings have also been made for patients The calibration of this differential transmission must be made by continuously recording radiation detectors introduced in the oesophagus (BENNER et coll 1959) The average transmission values for different directions through a patient and the transmission of the average thickness of the cross-section in the same directions agree within 7 % for the patients included in the group investigated

The error caused by the integration can therefore be neglected

SUMMARY

A device for simultaneous measurement of the transmission through a patient at different levels is described Correlation between target dose and transmission is obtained by measurements in phantoms as well as in patients The discrepancy in relation to conventional tissue-equivalent calculations are discussed

ZUSAMMENFASSUNG

Eine Vorrichtung für gleichzeitige Transmissionsmessungen in verschiedenen Ebenen eines Patienten wird beschrieben Korrelation zwischen der Herddosis und der Transmission wird durch Messungen in den Phantomen sowie in den Patienten erhalten Die Diskrepanz im Verhältnis zu den gewöhnlichen gewebeäquivalenten Bestimmungen wird diskutiert

RÉSUMÉ

L'auteur décrit un dispositif de mesures simultanées à différents niveaux de la transmission du rayonnement à travers le malade au cours de la roentgenthérapie rotatoire des tumeurs de l'oesophage Il obtient la corrélation entre la dose à la cible et la dose transmise par des mesures sur des fantomes et sur des malades L'auteur examine les discordances avec les calculs faits au moyen des équivalents de tissus habituels

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The last columns of Table 2 show the variation of scattered contribution along the field for three different transmissions calculated from corresponding variations of TAR When calculating the dose distribution, the variation of the primary beam intensity must also be considered

If the target doses, thus determined, are correlated with simultaneously measured doses in the oesophagus of different patients, there is very good agreement Fig 10 shows a dose distribution with the accustomed agreement between calculation and measurement in the patient

Target dose The TAR values valid for a homogeneous water equivalent thorax have been calculated from cross sections drawn at different levels of the patients included in this investigation This method results in an underestimation of the target dose, averaging 20 % (extreme values 0 and 40 %) Calculation of the target dose in homogeneous material by means of transmission measurements results however in an overestimation of the actual dose by between 20 and 40 %

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FROM THE DEPARTMENT OF ONCOLOGY, HADASSAH UNIVERSITY HOSPITAL
JERUSALEM ISRAEL

GASTRO INTESTINAL FUNCTION AFTER ABDOMINAL COBALT IRRADIATION

by

E RATZKOWSKI and A HOCHMAN

The gastro intestinal tract is notorious for its radiosensitivity Death due to *total* body irradiation is the consequence of damage to the haemopoietic system and with higher doses the digestive system The radiation effect on the gastro intestinal lining has been studied in animals by QUASTLER (1956), BOND (1950) CONRAD (1954 1956) and others Data relating to cell survival and the reparative capacity of the rat and mouse intestinal mucosa after continuous and single radiation exposure have been reported by QUASTLER et coll (1959) BLOOM (1950) WILSON (1964), and WIERNICK et coll (1966) Clinical observations *in human* gastro intestinal reactions following irradiation with injury and complications have been reported by ASHBAUGH et coll (1963), BROWN (1962) WOOD *et coll* (1963) ROSEN et coll (1964) GRAHAM et coll (1963) HALLS (1965) and others

During the last ten years isotope labelled substances such as ^{131}I labelled triolein and oleic acid and ^{131}I labelled polyvinylpyrrolidone have become available for the investigation of the absorptive capacity and permeability of the gastro intestinal mucosa following irradiation Few reports on the func

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ment schedules with field size 20 cm × 20 cm, or 20 cm × 16 cm, and 2 000 to 4 000 rad tissue dose, were as follows

	Number of patients
Whole abdomen	34
Lower abdomen (4 fields)	14
Lower abdomen (2 fields)	9
Upper abdomen (4 fields)	10
Upper abdomen (2 fields)	3
No irradiation	5

Method of investigation The following tests were carried out for an evaluation of the functional performance of the gastro intestinal tract

1 Absorption of vitamin B12 labelled by ^{60}Co (SHILLING 1963 test) Urinary excretion of more than 6 % of the orally administered dose was considered normal

2 Fat absorption studied by ^{131}I labelled triolein (SANDERS et coll 1956 REEVES et coll 1959 REITH et coll 1961) Fecal radioactivity expressed as percentage of the dose administered was determined and up to 3 % were considered as normal Blood radioactivity was defined as percentage of test dose per liter of whole blood

3 Determination of macromolecule passage through the intestinal wall protein loss by ^{131}I labelled polyvinylpyrrolidone (GORDON s 1959 PVP test) Up to 1 5 % of the administered dose found in the feces was considered normal

4 Gastric acid secretion After stimulation by the subcutaneous injection of 0 25 mg histamine the total acidity (normal 50 to 100 degrees) and free hydrochloric acid (normal 25 to 50 degrees) were determined

The patients were kept under close clinical observation during the investigation and controlled with blood counts biochemical examinations and the necessary roentgendiagnostic procedures

Clinical observations The patients in this series were seriously ill Large abdominal masses occasionally gave rise to partial obstruction or complete ileus Diarrhoea during or after treatment in ten patients was probably due to the irradiation Proctitis was recorded in two patients and in one patient cystitis in four patients cellulitis of the abdominal wall appeared some time after irradiation Two patients developed terminal signs of renal damage, possibly irradiation induced These clinical disturbances corresponded rarely with functional impairment as indicated by the tests Nearly all patients receiving

tional reaction of the gastro intestinal mucosa to therapeutic irradiation with telecobalt have been published, however (REEVES et coll 1963, 1965, GOODRICH et coll 1962)

The aim of the present investigation was to ascertain functional changes of the gastro intestinal tract in patients suffering from abdominal carcinomatosis who received telecobalt therapy, each received 2 000 to 4 000 rad homogenous irradiation to a large part of or to the whole abdomen

Material and Treatment Seventy five patients (67 females and 8 males) suffering from widespread malignancy of the abdomen were investigated The mean age was 50 1 (range 12—78) The diagnoses in the 75 patients were as follows

	Number of patients
Carcinoma of ovary	37
Carcinoma of uterus	5
Carcinoma of cervix	3
Generalized abdominal spread of unknown origin	4
Carcinoma of breast with general abdominal spread	4
Carcinoma of colon	3
Carcinoma of stomach	3
Carcinoma of rectosigmoid junction	2
Mesothelioma peritonei	1
Abdominal lymphoma	2
Splenic lymphoma	1
Reticulum cell sarcoma of stomach	1
Hodgkin s disease	4
Leiomyosarcoma	2
Neuroblastoma	1
Carcinoma of pancreas	2

In fifty five patients the diagnosis was established by laparotomy, in seven patients cytologically from aspirated abdominal fluid, in eleven patients by biopsy and in two on the clinical evidence The mean survival of fifty four patients was 23 months (median survival 13 months, range 2—228 months) Eighteen patients were alive 3 months to 13 years after the diagnosis was established, for three patients the survival time was unknown

The patients received cobalt 60 teletherapy in accordance with the clinical findings either to the lower or upper, or to the whole abdomen The treat

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Table 3

Results of Shilling test in relation to irradiated area and irradiation doses

Irradiation area	Irradiation dose 800—2 000 rad				Irradiation dose over 2 000 rad			
	Total number of tests	Number and abnormal tests	Mean excretion % of		Total number of tests	Number and abnormal tests	Mean excretion of	
			Abnormal tests	All tests			Abnormal tests	All tests
Lower abdomen	8	3 (36 5)	4 5	10 6	26	8 (30 8)	2 7	11.2
Upper abdomen	4	1 (25)	4 1	15 2	8	3 (37 5)	3 9	8 5
Whole abdomen					16	5 (31 3)	3 2	9 92

Table 4

Shilling tests repeated in the same patient

Results of repeated tests	Dose of radiation in rad			Time difference of 18 months between tests
	800—2 000 Difference between test and test	2 000—3 000 Dose difference	< 3 000 Dose difference	
No change	3	1	1	
From normal to abnormal	3	1		1
From higher to lower excretion	2	1		
From lower to higher excretion	2	1		

ed and often only one of the gastro intestinal functions could be investigated This made it difficult to arrive at an accurate evaluation of the results

Schilling test Seventy two tests were performed in 40 patients and twenty of these were abnormal (27 7 %) The results of the Schilling test at different radiation levels are given in Table 1, and the influence of the time interval after irradiation on B12 absorption is recorded in Table 2 The results of the Schilling test in relation to the irradiated area and the irradiation dose are given in Table 3

Of the nine Schilling tests performed before irradiation only four were repeated in the same patient during treatment two gave no change after

Table 1

Results of the Schilling test at different dose levels

Radiation rad	Total tests	Abnormal tests		Mean excretion in per cent	
		Number	Percentage	Abnormal tests	All tests
None	9	—	—	—	17 45 (range 7 4—35 6)
800—2 000	12	4	33 3	5 02	11 9 (range 4 1—35 5)
2 000—3 000	28	9	32 1	3 0	10 5 (range 0 5—23 7)
< 3 000	23	7	30 4	3 21	10 75 (range 1 5—25)

Table 2

Irradiation of abdominal cavity with 2 000 rad and more — Schilling test performed at different time intervals

Time after irradiation	Number of tests	Number abnormal	Percentage abnormal	Percentage mean excretion	
				Abnormal tests	All tests
Within a week	30	11	36 6	3 18	10 07 (range 0 5—25 0)
1 to 12 months after treatment	10	2	20	3 3	12 66 (range 2 4—23 7)
1 to 10 years after treatment	11	3	27 3	2 6	8 9 (range 1 5—15)

irradiation to the upper abdomen complained of anorexia or nausea, no marked clinical changes were recorded

Leucopenia was the main radiation induced complication, leading to protraction or interruption of the treatment This was particularly prominent in the irradiation of the lower abdomen Thirty patients receiving 3 000 rad to the lower abdomen had a mean leucocyte count at the beginning of the treatment of 6 744/mm³ but at the end of the treatment there was a mean drop of 42 5 %

The aim was to follow the patients during and after treatment and to establish the functional ability of the gastro intestinal tract before the commencement of therapy and following various doses of radiation The study was however carried out on very ill patients and treatment had often therefore to be started before any tests were possible Tests could sometimes not be repeat

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Results of Shilling test in relation to irradiated area and irradiation doses

Irradiation area	Irradiation dose 800—2 000 rad				Irradiation dose over 2 000 rad			
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Table 5

Fecal excretion of ^{125}I labelled triolein before irradiation and at different radiation levels

Irradiation rad	Mean fecal excretion %	Range %	Number of examinations	Number and % of abnormal tests	Mean fecal excretion in % of	
					Abnormal tests	Normal tests
All examinations	4 96	0 07—26 2	76	32 (42 1)	10 14	1 18
Before irradiation	4 28	0 2 —12 2	11	4 (36 3)	9 22	1 46
After 800 and over	5 08	0 07—15 6	65	28 (43)	10 2	1 14
600—1 000	6 57	0 4 —18 1	7	4 (57 1)	10 2	1 7
After 2 000	5 22	0 07—26 2	52	22 (42 3)	10 4	1 18
After 3 000 and over at least 3 months previously	3 88	0 07—10 8	15	7 (40 6)	6 9	1 23

Table 6

Results of ^{125}I labelled triolein excretion test in relation to the irradiated area — Irradiation dose 2 000 rad and over

Irradiated area	Number of tests	Number of abnormal tests	Per cent of abnormal tests	Mean excretion in per cent of		
				All tests	Abnormal tests	Normal tests
Lower abdomen	29	9	31	4 01	10 2	1 21
Upper abdomen	6	2	33 3	2 91	6 6	1 0
Whole abdomen	20	12	60	7 06	11 22	0 84

3 000 rad to the lower and 3 000 rad to the whole abdomen, in one test excretion of the isotope became abnormal after 3 500 rad to the upper abdomen, and in one it changed from 35 6 % to 13 6 % after 3 000 rad to the whole abdomen

Sixteen patients underwent B12 absorption examinations during treatment, the results of these are presented in Table 4

Six patients with abnormally low urinary excretion of the isotope were re examined with due regard to the intrinsic factor Three of these then had normal excretion, i e only three of the six patients suffered from malabsorption but the three others had enzyme deficiency

Table 7

Comparison of fat absorption responses at different radiation levels (changes in fecal excretion) in sixteen patients who underwent repeat examinations

	After dose differences of		Upper abdominal added to lower abdominal irradiation	After time interval of 2 to 6 months
	2 000—3 000 rad	Over 3 000 rad		
Normal a d no change	4		1	1
F om normal to abnormal	1		4	1
From abnormal to normal		1		2
Abnormal no change		1		

Table 8

Mean blood radioactivity in 64 patients after triolein test dose

K nd of pat ents examined	Number of examin ations	Mean radioactiv ty /l			Range per cent
		Mean after 4 hrs	Mean after 5 hrs	Mean peak within first 6 hrs	
All	64	2 43	2 68	2 80	0 7 —5 8
Pat ent w th normal fecal excr tion	36	2 52	2 61	2 88	0 9 —5 8
Pat ents w th abnormal f cal exc et on	27	2 26	2 52	2 6[illegible]	0 7 —5 61
Bef re rradiat on	6	2 31	2 8	2 8	0 98—4 6
Irrad ation 800 rad nd o er	57	? 07	2 62	? 77	0 7 —5 8
Irrad at on 2 000 rad and over	45	2 32	? 51	2 74	0 8 —5 5
3 000 rad and ove at least 3 months p ously	13	2 69	2 77	2 98	1 1 —5 61

[131]I labelled triolein fat absorption studies Examinations were carried out in 52 patients thirty seven of which (45 1 %) had an abnormally high fecal excre tion Twenty eight out of the fifty two patients (53 8 %) had fat malabsorption at some time during the investigation The mean fecal excretion in all the tests performed was 6 7 % with a range of 0 07 %—82 %

Among the 52 patients examined for fat absorption two were suffering from generalized abdominal lymphoma two from abdominal Hodgkin s disease and one patient from pancreatic carcinoma with spread into the gastric

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Fecal excretion of 125I labelled triolein before irradiation and at different radiation levels

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After 2 000	5 22	0 07—26 2	52	22 (42 3)	10 4	1 18
After 3 000 and over at least 3 months previously	3 88	0 07—10 8	15	7 (40 6)	6 9	1 23

Table 6

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Upper abdomen	6	2	33 3	2 91	6 6	1 0
Whole abdomen	20	12	60	7 06	11 22	0 84

3 000 rad to the lower and 3 000 rad to the whole abdomen, in one test excretion of the isotope became abnormal after 3 500 rad to the upper abdomen, and in one it changed from 35 6 % to 13 6 % after 3 000 rad to the whole abdomen

Sixteen patients underwent B12 absorption examinations during treatment, the results of these are presented in Table 4

Six patients with abnormally low urinary excretion of the isotope were re examined with due regard to the intrinsic factor Three of these then had normal excretion, i e only three of the six patients suffered from malabsorp tion but the three others had enzyme deficiency

Table 10

Gastric acid secretion at various radiation levels

Irradiation rad	Total acidity				Free acidity				Abnormal
	Normal	Hyper	Hypo	An acid	Normal	Hyper	Hypo	An acid	
None	4	2	1		4	2	1		3/7 42 8
800—2 000	1		7		1		5	2	7/8 87 5
2 000—3 000	5		6		5		2	4	6/11 54 5
Over 3 000	1		4	1	1		1	4	5/6 83 3
Total	11	2	18	1	11	2	9	10	21/32 65 6

32 abnormals 10 14 % (range 3 3 %—26 2 %) The fecal excretion of triolein at different radiation levels is recorded in Table 5

The fat absorption results in relation to the irradiated area are presented in Table 6

Four of the triolein examinations performed before irradiation, were repeated in the same patients after irradiation with 3 000 rad The fecal excretion in these four patients were before irradiation 2 5 % 0 7 % 5 7 % and 0 4 % respectively The repeat triolein tests gave the following values 14 1 % 1 8 % 26 2 % and 0 2 % respectively

Sixteen patients were re examined during and after irradiation the doses employed ranging from 1 000 to 4 000 rad The fat absorption responses according to the triolein test are given in Table 7 Nine patients suffered from diarrhoea and one from proctitis during or after treatment six of these had at some time abnormal fecal triolein excretion while in four patients the test was within normal limits

The blood radioactivity was determined in 64 patients the mean peak value during the first 6 hours after the test meal for all patients being 2 08 %/l Nineteen patients reached the maximum level within 4 hours thirty three within 5 hours and twelve patients within 6 hours The blood radioactivity in patients with normal and abnormal fecal excretion at different doses is summarized in Table 8

Six examinations were carried out in the five patients excluded (four patients with abdominal lymphatic disease and one with carcinoma of the

Table 9

Fecal PVP excretion radiation dose and clinical data in five patients with protein loss

Case	Excretion %	Irradiation dose rad	Clinical data
1	1 6	2 000 to lower abdomen	Generalized abdominal malignancy of ovarian origin some diarrhoea during treatment proteins normal
	0,9	3 000 to lower 1 800 to upper abdomen	
28	6	2 100 to lower abdomen	Generalized abdominal malignancy of ovarian origin poor general condition during treatment septic temperature
38	0 5	1 400 to lower abdomen	Abdominal malignancy due to ovarian carcinoma good general condition at beginning of treatment albumin/globulin ratio 3 8/2 8
	4 5	3 000 to lower 2 000 to upper abdomen	Two weeks after treatment severe diarrhoea death at 6 months after treatment from uremia probable renal damage albumin/globulin ratio 3 8/2 6
40	1 9	Before irradiation	Generalized abdominal lymphoma cachexia diarrhoea albumin/globulin ratio 2 9/2 8
	0 25	2 000 to lower abdomen	No improvement
45	0 6	3 000 to lower abdomen	Carcinoma of rectosigmoid junction 50 cm of large bowel resected
	0 03	3 000 to lower 2 000 to upper abdomen	
	4 9	5 500 to lower 2 400 to upper abdomen	Diarrhoea during treatment

lumen and bowel The prominent symptom of three of these patients was persistent diarrhoea

Intestinal lymphoma is frequently associated with fat malabsorption, as has been described in a number of reports (Gough et coll 1962, Sprackles 1963 Ramot et coll 1965) Five patients were therefore excluded from the study since they were considered unsuitable for assessing radiation induced functional changes The results of the examinations of these five patients will however be given separately below

Seventy six triolein examinations were carried out in the remaining 47 patients, and thirty two of these (42 1 %) were abnormal The mean fecal excretion of all the 76 tests was 4 96 % (range 0 07 %—26 2 %) The mean fecal excretion in 44 normal tests was 1 18 % (range 0 07 %—3 %), and in the

for the intestinal mucosa Animal experiments are made with continuous exposure or with large single exposures at different dose levels and cannot be compared with fractionated and protracted therapy in human subjects

In evaluating the present study we met with another difficulty Only a limited number of baseline data (pre treatment levels) for our own patients could be obtained the reasons being given above Moreover, progress of the disease or its improvement following treatment are factors likely to influence the performance of the gastro-intestinal tract and have to be taken into consideration The data obtained in this study seem however to permit reliable conclusions as to whether therapeutic cobalt irradiation causes severe impairment of the gastro-intestinal function or not No severe clinical side effects were observed apart from leukopenia which produced no serious haematologic complications

B12 absorption Irradiation caused impairment of the B12 absorption (Table 1) in about a third of the patients with rising dose levels impairment in these susceptible patients increased as shown by the mean abnormal urinary excretion which fell from 5 02 % to 3 %

The time factor (Table 2) appears to have some influence as the percentage of patients affected by B12 absorption disturbance fell to less than 25 % a month after cessation of therapy the severity of impairment did not alter

What part of the abdomen was irradiated had no influence on the B12 absorption (Table 3) but again higher dose levels caused more severe disturbances Furthermore repeated Schilling tests indicated that added radiation doses affected the B12 absorption in more than 30 % of the patients (Table 4) Because of the small number of tests modified by the intrinsic factor no conclusion can be drawn as to whether enzyme deficiency can be caused by irradiation

Fat absorption It is more difficult to judge the results of the fat absorption examinations since four (36 3 %) of the eleven tests performed before treatment was started were abnormal Tables 5 6 and 7 suggest however that fat absorption impairment be caused by irradiation within the therapeutic dose range in about 25 % of the patients

The tabulated data further indicate (1) that the mean fecal excretion of the isotope is considerably higher after than before irradiation (2) the mean fecal excretion of patients with fat malabsorption is higher after irradiation than before (3) the percentage of abnormal tests is higher after irradiation than before the peak being in the dose range 600 to 1 000 rad (4) three months after irradiation the percentage of abnormal tests does not change much but

pancreas), the mean fecal excretion was 28 7 % Four of the tests were performed before irradiation, one after 2 000 rad (9 3 %) and one after 3 500 rad (1 9 %) The blood radioactivity was determined in four of the patients The one patient, with normal fecal excretion, had the same blood radioactivity (2 5 %/l and 2 8 %/l) as was noted earlier in the other patients (see p 423) The three patients with severe fat malabsorption had a much lower blood radioactivity, the mean peak being at 4 hours 0 85 %/l, at 5 hours 1 41 %/l, and at 6 hours 1 54 %/l

PVP test as an indicator of protein loss from the digestive tract Fifty one PVP examinations were carried out in 39 patients, five tests (9 8 %) indicated abnormally high fecal excretion of isotope The mean fecal excretion in all the 51 examinations was 0 84 % (range 0 03 %—6 %) In the 46 normal tests, the mean fecal excretion was 0 52 % (range 0 03 %—1 5 %), in the five abnormal tests 3 7 % (range 1 6 %—6 %)

Repeat PVP tests were performed in 10 patients including four patients who at some time of the investigation had abnormal permeability of the gastro intestinal mucosa for macromolecules The results of the various tests in patients, representing protein loss, radiation doses and clinical details, are summed up in Table 9

Gastric acid secretion Thirty two gastric acid examinations were carried out in 24 patients, twenty one of the examinations (65 6 %) revealing abnormal values The total acidity tests in these patients revealed hyperacidity in 2, hypoacidity in 18, and anacidity in one patient, while the free acidity tests disclosed hyperacidity in 2, hypoacidity in 9, and anacidity in 10 patients

Correlation of the various irradiation doses to gastric acid secretion rendered the results reported in Table 10 The gastric acid examinations were repeated in six patients Further irradiation diminished the gastric acid secretion The gastric acidity returned to normal 6 months after irradiation in one patient

The four tests (Schilling, triolein, PVP gastric acid secretion) were, as previously mentioned, carried out in 75 patients In 4 patients, all four of the tests, in 26 three, and in 14 patients two of the tests were applied, and sixteen out of 47 patients (34 %) had gastro intestinal dysfunction proven by different parameters

Discussion

No series of normal healthy people can receive high doses of abdominal irradiation for comparison, and investigations in irradiated healthy animals can be correlated only in so far as they demonstrate a good recovery potential

for the intestinal mucosa Animal experiments are made with continuous exposure or with large single exposures at different dose levels, and cannot be compared with fractionated and protracted therapy in human subjects

In evaluating the present study we met with another difficulty Only a limited number of baseline data (pre treatment levels) for our own patients could be obtained the reasons being given above Moreover, progress of the disease or its improvement following treatment are factors likely to influence the performance of the gastro intestinal tract and have to be taken into consideration The data obtained in this study seem however to permit reliable conclusions as to whether therapeutic cobalt irradiation causes severe impairment of the gastro intestinal function or not No severe clinical side effects were observed apart from leukopenia which produced no serious haematologic complications

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the mean fecal excretion in the abnormal tests in much lower, perhaps indicating recovery The follow-up examinations were however insufficient in number to determine recovery or delayed effects of irradiation on fat absorption

The highest percentage of abnormal examinations and the highest mean abnormal excretion occurred after irradiation of the whole abdomen

Some comparable data appear in the literature SANDERS et coll (1956) found transient malabsorption in 13 out of 29 patients after 200 kV roentgen irradiation within a dose range of 945 to 3 100 R, the highest incidence *occurring during the third week after 2 000 R* REEVES *et coll* (1959, 1963) confirmed the incidence of fat malabsorption after irradiation, with a greater percentage of abnormal tests after telecobalt than after conventional therapy, the authors reported the majority of abnormal triolein absorption tests after 2 000 rad and during the third week of therapy The investigations of GOODRICH et coll (1962) indicated a very low incidence of fat malabsorption as determined by the oleic ^{131}I absorption tests, only the lower abdomen was irradiated in these studies

The mean blood radioactivity as well as the mean peak blood values (according to Table 8) were within the normal range even in patients with abnormal fecal triolein excretion It has been pointed out by many authors (CORREIA *et coll* 1963, ISLEY *et coll* 1963, REEVES *et coll* 1963) *that fecal triolein* excretion is a more reliable indicator of fat absorption disturbance than blood radioactivity

Very low blood levels have been described as significant of *triolein* malabsorption (CORREIA et coll), an observation confirmed in the patients of the present series with abdominal lymphoma and pancreas carcinoma Not only did these patients have a much higher fecal triolein excretion than all the other patients, but their blood radioactivity was significantly lower, 0 85 %/l as against 2 85 %/l

Protein absorption Only 9 8 % of the PVP examinations gave abnormal results, suggesting that the macromolecule passage through the mucosal barrier is only rarely affected by irradiation The analysis of the abnormal results (Table 9) indicates that Case 1 improved with additional irradiation Case 38, a patient who died from uremia following irradiation, might have had a particular hypersensitivity affecting not only the gastro intestinal tract Case 40 was one of the lymphoma patients excluded from the evaluation of fat absorption, he *failed to improve clinically after irradiation* but according to the PVP test no longer suffered from macromolecule loss Case 45 developed abnormal fecal excretion only after a high irradiation dose, resection of a large

part of the bowel must however be considered as a contributory cause of malabsorption in this instance

We have found no comparable investigations in human subjects in the literature in animal experiments radiation caused protein loss through the gastro intestinal wall in the dose range 250 to 1 000 rad (SULLIVAN 1960)

Gastric acid secretion The influence of irradiation on the gastric acid secretion has been recognized for many decades (CASE et coll 1928 PALMER et coll 1939) and as doses of 1 000 to 2 500 R have produced transient anacidity in two thirds of patients this radiation effect has been used as treatment in peptic ulceration (RICKETS et coll 1948) About two-thirds of the present examinations had abnormal values (Table 10) but as differences at various radiation levels were insignificant no dose relationship could be established as little as 800 rad however induced hypoacidity Gastric acidity returned to normal in one patient 6 months after 3 000 rad The point of recovery has not been especially investigated in this study as it has been established previously

When evaluating the results of the four different tests, a differential radiosensitivity of the gastro intestinal tract in its absorptive capacity for various substances appears to exist B12 and fat absorption are more often impaired than protein absorption These conclusions are supported by the multiple investigations carried out in the same patients Gastric acid secretion is easily influenced by irradiation, but the relation to the other tests could not be established directly in the study as gastric secretion was often the sole test carried out in a given patient

The relatively minor functional impairment of the gastro-intestinal tract in the human material corresponds well with observations in animal experiments on intestinal cell survival and irradiation response QUASTLER et coll (1959) demonstrated experimentally that the intestinal mucosa of the rat at dose rates up to 415 rad per day maintained normal crypt size generation time and mature cell life span, at 415 rad per day however, the percentage of proliferating cells diminished This steady state failed to change with a continuation of the irradiation and it is quite possible that no functional disturbance ensued WILSON (1964) interpreted the experimental results of QUASTLER on the basis of cell survival data and reached the same results as the latter by calculation WIERNICK (1966) studied the effect of various fractionated irradiation regimes in human subjects by jejunal biopsies after a single dose of 1 000 rad the intestinal mucosa was damaged beyond repair This corresponds with the threshold dose reported by QUASTLER (1956) and QUASTLER & ZUCKER (1959) causing the intestinal syndrome I and intestinal syndrome II and the death of the animal With two weekly doses of 500 R

and six treatments spread over 18 or 19 days, WIERNICK et coll (1966) obtained progressive recovery of the jejunal mucosa in human subjects He proposed a fractionation method consisting of large doses spread in such a way as to enable sufficient recovery of the intestinal lining and controlled by repeated biopsies He hoped thereby to produce greater tumour destruction

All these investigations did not deal with the functional state of the gastro intestinal tract but they explain why therapeutic telecobalt irradiation according to our results gave rise to an impairment of the gastro intestinal functional capacity, which generally resulted in only mild disturbances in a limited number of patients This negative finding is of practical importance as it enables the continuation of an effective palliative treatment measure The results may perhaps be further improved by larger fractionations controlled by repeated biopsies and functional studies

Conclusions

Seventy five patients with generalized abdominal malignancy were given therapeutic telecobalt irradiation to a part or the whole of the abdomen with 2 000 to 4 000 rad The functioning condition of the gastro intestinal mucosa was studied by B12 absorption, triolein absorption, PVP and gastric acid secretion tests

The B12 absorption was impaired in about one third of the patients to a degree directly related to the dose The number of patients affected began to diminish one month after the cessation of treatment The fecal triolein excretion was high in about 25 per cent of the patients, the peak excretion being in the dose range 600 to 1 000 rad The greatest percentage of abnormal tests and highest mean abnormal fecal excretion were noted after the irradiation of the whole abdominal cavity The blood radioactivity was not a sensitive indicator of fat malabsorption The PVP test revealed almost no macromolecule loss through the gastro intestinal mucosa in the therapeutic dose ranges The gastric acid secretion was diminished in about two thirds of the patients after more than 800 rad but the restoration to normal acid levels occurred in most of them

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SUMMARY

Therapeutic telecobalt irradiation with 2 000 to 4 000 rad was administered in 75 patients with generalized abdominal malignancy *The effect upon the intestinal mucosa* as indicated by the B_{12} absorption triolein absorption PVP and gastric acid secretion tests is discussed

ZUSAMMENFASSUNG

Telekobaltbestrahlung von 75 Patienten mit generalisierter abdomineller Malignität wurde mit Dosen von 2 000 bis 4 000 rad vorgenommen. Der Einfluss der Bestrahlung auf die Darmschleimhaut mit Bezug auf die Vitamin B_{12} Absorption, Trioleinabsorption, PVP und die Sekretion der Magensäure wird diskutiert.

RÉSUMÉ

Une série de 75 malades atteints d'affection maligne généralisée de l'abdomen ont été traités par télécobalt thérapie par des doses de 2 000 à 4 000 rad. Les auteurs en ont étudié l'effet sur la muqueuse intestinale au moyen de l'absorption de la vitamine B_{12}, l'absorption de la trioléine, de PVP et par des épreuves de la sécrétion acide gastrique.

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FROM THE RADIOTHERAPY CLINIC (DIRECTOR PROF L R HOLSTI) UNIVERSITY CENTRAL HOSPITAL, HELSINKI FINLAND

AUTOPSY FINDINGS IN LUNG CANCER TREATED WITH MEGAVOLTAGE RADIOTHERAPY

by

P M RISSANEN U TIKKA and L R HOLSTI

The many advantages of megavoltage therapy have led to its increasing use during the last decade in radiotherapy of inoperable pulmonary carcinoma The clinical experience obtained so far has not been very favourable however For instance GUTTMANN (1958) achieved a one year survival rate of 33 per cent and a two-year survival rate of 9 per cent Many other authors (HAAS et coll 1957 KUTZ 1958 COCCHI 1961 1964, BELING & EINHORN 1965 HOLSTI 1965 1967a DEELEY 1967) have presented survival rates in roughly the same range GUTTMANN (1964) reported slightly better results with megavoltage therapy after exploratory thoracotomy although WATSON (1956) was considerably more pessimistic

There are fairly few studies of the effects of megavoltage therapy on carcinoma of the lung based on autopsy materials Five of WATSON's (1956) cases were examined post mortem and all of them had residual primary malignancy GUTTMANN (1958) established three complete local cures (16 per cent) in an autopsy material of 19 cases Four cures were claimed by HAAS et coll (1957) following autopsies performed in seven cases BELING & EINHORN (1965) stated that autopsy revealed malignant tissue at the primary site in 48 of their 50 cases

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The purpose of the present study was to establish from an autopsy material whether megavoltage therapy in the conventional dosage is capable of destroying primary lung carcinoma In addition, special attention was paid to the cause of death in such cases

Material and Methods The material comprised 67 histologically verified cases of inoperable carcinoma of the lung treated during the period 1963—1967 by megavoltage therapy and examined by autopsy 2 months to 4 years and 1 month (average 9 months) later A total of about 1 400 cases of pulmonary carcinoma were treated at the clinic during the period The histologic type was verified prior to treatment by biopsy in connection with bronchoscopy, tumour puncture, mediastinoscopy, scalenus biopsy or thoracotomy Together with roentgenography these methods were used also to determine the size and localization of the growth

Eight cases had meta tases in the lymph nodes of the supraclavicular fossa or the neck, eighteen in the mediastinum, and three elsewhere (brain, liver) at the beginning of therapy Of those treated, forty five were regarded as inoperable because of the size, central site, or metastases and five on account of the general condition (poor respiratory function, other lung conditions, cardiac disease) Nine cases were considered to be inoperable after exploratory thoracotomy, and in eight cases partial resection of the tumour was performed

Forty six cases were treated with 33 MeV photons and twenty one with a 3 000 curie ^{60}Co unit The commonest field size was 6 to 10 cm×10 to 12 cm Mostly, 2 fields were used in photon therapy and 3 or 4 fields in ^{60}Co therapy

The tumour dosage ranged from 4 000 to 7 000 rad over 5 to 10 weeks but was usually 4 500 to 5 500 rad over 5 to 8 weeks Individual treatment planning was the rule, the aim in all treatments being to achieve a homogeneous dose distribution in the treatment volume Thirty eight cases were treated with split course therapy (HOLSTI 1966, 1967b) and twenty nine cases continuously The total tumour dose in the former was roughly 10 per cent higher than in the continuous treatment (HOLSTI 1967b) The treatment was repeatedly interrupted because of e g poor general condition pyrexia inflammation and anemia in seven cases, complicating factors in three cases prolonged the treatment time to between 114 and 133 days Therapy had to be discontinued in seven cases at 2 000 to 3 000 rad on account of the general condition Sixty cases received the planned therapeutic dose

The whole material of 67 cases was histologically distributed as follows squamous cell carcinoma in 29 anaplastic carcinoma in 16 small cell carcinoma in 17, unclassified carcinoma in 3 and adenocarcinoma in 2 cases

The mean survival time in the series was nine months Forty four of the total series died of carcinoma or metastases, and twenty three from other causes (nine

Table 1

No carcinoma tissue at primary tumour site

Type of tumour	Split-course	Continuous	Total
Squamous cell carcinoma	6	1	7
Anaplastic carcinoma	2	—	2
Small cell carcinoma	4	2	6
Unclassified carcinoma	1	1	2
Adenocarcinoma	1	—	1
Total	14	4	18

Table 2

Islets of carcinoma cells in the fibrotic area at the site of the primary tumour

Type of tumour	Split course	Continuous	Total
Squamous cell carcinoma	1	3	4
Anaplastic carcinoma	1	4	5
Small cell carcinoma	2	3	5
Unclassified carcinoma	—	—	—
Adenocarcinoma	—	—	—
Total	4	10	14

from *pneumonia* eight from *cardiac failure* and *four* from a pulmonary embolus one patient committed suicide and one died in an accident)

Results

The findings have been divided into four groups according to the type of primary growth at autopsy (1) no carcinomatous tissue evident (2) no definite malignancy macroscopically but *microscopically* fibrosis with obvious islets of carcinoma cells (3) necrotic areas with malignant infiltration and (4) viable malignant tissue in the treatment area

1 *No carcinomatous tissue* Eighteen cases of the total series (18/60=30 per cent) had no carcinomatous tissue in the treatment area either macro- or microscopically The distribution of the cases in this group by the histologic appearances appears in Table 1

Partial resection of the growth was performed in six and exploratory thoracotomy in two of these eighteen cases The tumour size in this group prior to

Table 3

Necrotic area with carcinomatous tissue (brackets = treatment not completed)

Type of tumour	Split course	Continuous	Total
Squamous cell carcinoma	3	2 (1)	5
Anaplastic carcinoma	1	2 (1)	3
Small cell carcinoma	1 (1)	—	1
Unclassified carcinoma	—	—	—
Adenocarcinoma	—	—	—
Total	5	4	9

Table 4

Viable tumour tissue in the treatment area (brackets = treatment not completed)

Type of tumour	Split course	Continuous	Total
Squamous cell carcinoma	7	6 (2)	13
Anaplastic carcinoma	3	3 (1)	6
Small cell carcinoma	3	2 (1)	5
Unclassified carcinoma	1	—	1
Adenocarcinoma	1	—	1
Total	15	11	26

treatment was 3 to 8 cm in diameter, usually 4 to 7 cm, the tumour dose was 4 800 to 6 250 rad Fourteen (78 per cent) cases of this group were treated by the split course method and four received the entire course of irradiation as continuous therapy No cytostatics were used The pre planned treatment scheme was fulfilled in all the cases and there were no complications The condition of these eighteen cases appeared to be distinctly improved at the roentgenologic control performed after the termination of therapy Eight patients died from distant metastases, and ten of some other cause, such as pneumonia, cardiac failure or pulmonary embolus

2 *Fibrosis with islets of carcinoma cells* The fourteen (14/60=23 per cent) cases in this group are recorded histologically in Table 2

Partial resection of the tumour was performed in one and exploratory thoraco tomy in another of these cases The growth was 4 to 8 cm in diameter and the dosage 4 700 to 7 000 rad Cytostatics were also administered in three cases Four of the cases were treated by the split course method and ten received con tinuous irradiation The treatment was completed according to the therapeutic

Table 5

Localization of the metastases established at autopsy of 56 cases

Lymph nodes (ncluding mediastinal and paratracheal lymph nodes)	34
Liver	30
Adrenals	27
Brain	22
K dneys	20
Pancreas	19
Skeleton	16
Lungs	14
Abdominal cavity	9
Thyro d gland	7
Other	18

scheme in twelve cases and in the other two was interrupted because of com plications (fever anemia etc) The condition in twelve cases was improved roentgenologically at the end of therapy while in two cases no change was ob erved The cause of death was distant metastases in eleven cases and other conditions in three cases

3 *Necrotic areas containing carcinomatous tissue* The group comprised nine cases Treatment had to be discontinued in three leaving only six (6/60=10 per cent) cases that received the planned dosage The distribution of the cases his tologically appears in Table 3

Three cases were subjected to exploratory thoracotomy The average diameter of the mass in this group was 6 to 9 cm the radiation dosage being 4 000 to 5 900 rad In only three cases was it possible to complete the therapeutic course according to schedule Six cases had complications (e g anemia fever) neces itating interruption in the therapy Five cases were managed by the split-course method and four cases received continuous treatment Four cases were given cytostatics in addition to radiotherapy Two cases were improved roentgeno logically after the termination of the therapy and in the remaining seven cases there was no definite change Seven patients died from distant metastases and two from other causes It is possible that the treatment volume was too small in two of the cases in this group

4 *I iable carcinoma tissue in the treatment area* The fourth group comprised 26 cases Treatment had to be discontinued in four of them and thus viable carcinomatous tissue was demonstrable both macroscopically and microscopically in the treatment area in 22/60 cases i e 37 per cent of those that received roughly the planned dosage The histologic distribution is given in Table 4

Table 6

Correlation between autopsy findings and radiation dose

	> 4 000 rad	> 5 000 rad	> 6 000 rad	Total
No carcinoma	8	8	2	18
Fibrosis	3	7	4	14
Necrosis	4	2	—	6
Viable carcinoma	6	11	5	22
Total	21	28	11	60

Exploratory thoracotomy was performed in three cases and partial resection of the tumour in one case the growth was 6 to 9 cm in diameter and the dosage 4 000 to 6 000 rad The split course technique was employed in fifteen cases and continuous radiotherapy in eleven cases The therapy was completed according to schedule in only thirteen cases, and in the other thirteen complications (anemia, fever, etc) interfered and in three of the latter cases prolonged the treatment time to 114—133 days

Roentgenography at the termination of the primary treatment indicated improvement in seventeen and no obvious change in nine cases A recurrence was observed roentgenologically in four cases 3 to 6 months after the primary therapy The treatment fields may have been too small or the tumour may not have been precisely localized in these cases One of the cases was treated with cobalt 60 therapy with the breathing of pure oxygen 20 minutes prior to therapy and during it The fractionation was 600 rad twice a week total dosage 4 700 rad/54 days (split course technique)

Nineteen of the patients in this group died of the primary disease or distant metastases Seven patients died from other causes

Metastases were demonstrated in fifty six cases of the total autopsy material the locations appear in Table 5 The ratio between the autopsy finding and the radiation dose is given in Table 6

Discussion

The prognosis of inoperable carcinoma of the lung treated with radiotherapy is generally considered to be poor (e g GUTTMANN 1955 1958 1961 HAAS et coll 1957, KUTZ 1958 COCCHI 1961, 1964, BELING & EINHORN 1965 HOLSTI 1965, 1967a) Some authors are completely pessimistic about the treatment (WATSON 1956) Almost invariably the starting point for radiotherapy is unfavourable The tumour is often of considerable size, as well as infiltrating, and thus inoperable The subjects are frequently elderly in poor condition and anemic,

Table 7

Autopsy findings and histologic features in the split-course group

	Squamous cell carcinoma	Anaplastic carcinoma	Small cell carcinoma	Unclassified carcinoma	Adenocarcinoma	Total
No carcinoma tissue	6	2	4	1	1	14
Fibrosis + carcinoma	1	1	2	—	—	4
Necrosis + carcinoma	3	1	1	—	—	5
Viable carcinoma tissue	7	3	3	1	1	15
Metastases	12/(17)	5/(7)	10/(10)	1/(2)	1/(2)	29/(38)

Table 8

Autopsy findings and histologic features in the continuous therapy group

	Squamous cell carcinoma	Anaplastic carcinoma	Small cell carcinoma	Unclassified carcinoma	Adenocarcinoma	Total
No carcinoma tissue	1	—	2	1	—	4
Fibrosis + carcinoma	3	4	3	—	—	10
Necrosis + carcinoma	2	2	—	—	—	4
Viable carcinoma tissue	6	3	2	—	—	11
Metastases	11/(12)	8/(9)	7/(7)	1/(1)	—	27/(29)

with infection as a prominent feature In addition metastases are often already present However in the present material which was of a wholly random character the carcinoma had actually disappeared microscopically in eighteen (30 per cent) of the cases that received the full planned therapy of at least 4 800 rad There were no complicating factors in these cases Fourteen (78 per cent) of these cases were treated by the split course technique which suggests that the method has definite advantages Bearing in mind that there was no true random selection of cases for split course or continuous therapy in this series comparison of the two methods (Tables 7 and 8) indicate that the primary tumour disappeared completely in 37 per cent of the cases treated by the former and in only 14 per cent of those treated by the latter method

Both macroscopic and microscopic regression frequently occurs during the interval of the split course therapy (HOLSTI 1967c) which may contribute to the good end result Metastases were encountered in 76 per cent of the cases treated by the split course technique and in 93 per cent of those given continuous therapy

The distribution of the metastases in the total material concurred on the

whole with that reported by ROSENBLATT & LISA (1956) All the cases with complete loss of malignant tissue had received over 4 800 rad Fourteen cases (23 per cent) had islets of carcinoma cells in the fibrotic areas Recurrence might well arise from such residual foci, as has been stressed in radiobiologic studies based on cell survival observations (FOWLER 1966) In those groups in which *viable carcinomatous tissue, or necrotic areas with islets of malignancy*, were found at autopsy in the therapeutic area, over half the number of cases (67 per cent in group 3, 50 per cent in group 4) had complications during therapy This prevented the realisation of the radiotherapeutic plan and thus impaired the end results

The treatment had to be interrupted in seven cases by the time the patients had received 2 000 to 3 000 rad All still showed evidence of malignancy, in three of the cases in addition to necrotic tissue The dose administered had obviously been incapable of destroying the tumour tissue Prolongation of the treatment time on account of protracted or recurrent complications, such as pyrexia or anemia, considerably hinders the chances of recovery

However, it was only in a few rare cases in which the therapeutic programme could be completed without noteworthy complicating factors (at a dosage of 4 000 to 6 000 rad) that viable carcinomatous tissue was demonstrated Only the individual radiosensitivity of the tumour can properly account for this, an important factor being the anoxic cells THOMLINSON & GRAY (1955) in pulmonary carcinoma in human subjects, regularly observed small necrotic anoxic areas more than 180 μ from the nearest capillary The proportion of anoxic cells in tumours is extremely important in relation to the radiation dosage needed for radical treatment and can make all the difference between success and failure (FOWLER et coll 1963) *Viewed against this background, it is perhaps not always most purposeful to aim at homogeneous dose distribution in radiation therapy* Anoxic areas need larger doses than well oxygenated areas The roentgenologic appearances were improved in 18 18 cases in group 1, in 12 14 cases in group 2, in 2/9 cases in group 3 and in 17/26 cases in group 4 These observations suggest that roentgenologic evidence of decrease or disappearance of the growth is an indication that local control of tumour is possible

Obviously, the smaller the tumour, the greater are the chances of success This is borne out too by the fact that the fully healed cases included six that had been subjected to palliative surgery But even if the tumour is destroyed completely, latent or subsequent metastases may impair the end result so that the final clinical results deteriorate as the patient succumbs to the metastases In any event it would appear that it is possible under favourable conditions to destroy the primary focus of pulmonary carcinoma by megavoltage therapy at a dosage of 4 800 to 6 000 rad

In summary two-thirds of the patients in the present material died of the primary growth or metastases In eighteen cases i e 30 per cent the tumour was sterilized by radiotherapy and the patients died from other diseases though eight of these even had distant metastases The study confirms the view that the greatest problem in the treatment of carcinoma of the lung is its readiness to form metastases The individual radiosensitivity of the tumours (e g the number of anoxic cells) obviously also play an important role

Acknowledgement

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SUMMARY

The autopsy findings in 67 cases of inoperable carcinoma of the lung treated with mega voltage therapy were analysed to determine whether the primary tumour had been destroyed Seventy eight per cent of the cases of complete cure had been treated by the split course technique Forty four of the total of 67 patients i e 66 per cent died from the original condition or metastases and twenty three (34 per cent) from other causes

ZUSAMMENFASSUNG

Die Autopsiebefunde in 67 Fallen von nicht operierbaren Lungenkarzinomen wurden analysiert um festzustellen ob der Primartumor vollstandig durch die Megavolt Rontgen bestrahlung zerstort wurde In 78 % der Falle die mit unterbrochener Serienbestrahlung behandelt wurden konnte eine vollstandige Heilung erreicht werden Primartumore oder Metastasen verursachten den Tod in 66 % (44 Patienten) wahrend 34 % (23 Patienten) infolge anderer Ursachen starben

RÉSUMÉ

Les auteurs ont etudie les resultats d autopsie de 67 cas de cancer du poumon inoperable traites par radiothérapie a mega voltage pour savoir si la tumeur primitive avait ete detruite Soixante dix huit pour cent des cas de guérison complète avaient ete traites par la technique de fractionnement du traitement (split course) Quarante quatre des malades sur un total de 67 c est à dire 66 pour cent sont morts du cancer primitif ou de metastases et 23 (34 pour cent) ont morts d autres affections

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SOME EFFECTS OF DATA ERROR IN THE ANALYSIS OF RADIOTRACER DATA

by

J MYHILL

Radioactive tracers have been used extensively to study some aspects of biological function in man The results of a radiotracer study may often be a *series* of measurements of radioactivity extending over an interval of time after administration of the radioisotope It is sometimes appropriate to represent the aspects which are under investigation by a *simplified* compartmental model and to fit the solution function of the model to the experimental data points in order to estimate the model parameters If the system is in a steady state then it has been previously shown that the behaviour of labelled substances can be represented by linear differential equations (SHEPPARD & HOUSEHOLDER 1951 BERMAN & SCHOENFELD 1956) and that the solution for the activity versus time curve in each compartment consists of a sum of exponentials

$$f(t)=\sum_{i=1} A_i e^{-\lambda_i t}$$

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How the errors and omissions in the data affect the estimation of the rate constants, λ_i, and the amplitudes, N_i, and through them the estimation of the transfer rates and compartment sizes, has recently become a subject of study (MYHILL, WADSWORTH & BROWNELL 1965, MYHILL 1965, 1966, 1967 a c)

The collection of data is usually terminated for some experimental reason The radioactivity may become too low to count accurately, the patient may become unavailable for study, or the radioactive label may become detached from its compound This data truncation, together with the experimental error in each measured data point and the fewness of points, creates uncertainty in the values of the model parameters This is the case even where a valid, unequivocal model of the system is assured

Method of error analysis

1 *Computer simulation of data* Data points were simulated on a high speed digital computer (English Electric KDF 9) using the equation for $f(t)$ and some random number generators The details of the simulation have been previously described (MYHILL 1968)

The situations where λ_1/λ_2 equals 10, 6, 4 and 2 were studied, the cases where the rate constants λ_i are closer to equality being the more difficult If λ_1/λ_2 is less than about four, some methods of analysis become less effective (BROWNELL & CALLAHAN 1963) or are subject to large bias (MYHILL, WADSWORTH & BROWNELL 1965) The ratio N_1/N was set equal to 10, 6, 4, 2 or 1 The special case of $N_1/N_2 = \lambda_1/\lambda_2$ has been previously reported (MYHILL 1967c) The simulated data were terminated when the value of the last data point was 5 % of the value of the initial point This corresponds to a situation often observed in reports of experiments and is a more difficult case to analyse than if the data were further extended in time (i e so that the value of the last data point was less) In an endeavour to approximate to types of data seen in the literature, the cases of 31 and 11 data points equally spaced over the time interval of data collection, or else equally spaced in log time (more points taken over the early portions of the data), were investigated Random error with a constant per cent standard deviation was simulated at each point The statistical distribution of the error was normal since it had been shown previously that the form of the statistical distribution of the error was of minor importance (MYHILL 1967, 1968) and the magnitude of the standard deviation of error in a data point in any one set of data was varied from 0 5 % to 10 % between sets The type of data simulated is shown in Figs 1 and 2 (continuous curves shown there without random errors added)

Table 1

Maximum amount of error in the data that allows convergence

Ratio of rate constants λ_i/λ_j	Ratio of amplitudes A_i/A_j	Number of data points 11 Equal spacing	11 Log equal spacing	31 Equal spacing	31 Log-equal spacing
10/1	6/1	10	10	10	10
10/1	4/1	10	10	10	10
10/1	2/1	10	10	10	10
10/1	1/1	*	*	10	10
6/1	10/1	3	1	6	3
6/1	4/1	10	7	10	10
6/1	2/1	10	10	10	10
6/1	1/1	*		9	10
4/1	10/1	1	0 5	2	2
4/1	6/1	4	1	6	3
4/1	2/1	8	4	10	8
4/1	1/1	*	*	10	8
2/1	10/1			0 5	**
2/1	6/1	*	*	0 5	0 5
2/1	4/1		*	1	0 5
2/1	1/1	*		2	1

The error entered in the table is the percentage standard deviation at a data po nt The error was normally distributed and of constant percent standard deviation throughout a set of data Th d ta were terminated such that the value of the last data point was 5 of the value of the first data point The maximum pe cent data error employed was 10

* Th s comb nation of cond tions was not simulated

** For convergence usi g these simple methods require an error less than 0 5

2 *Numerical analysis of simulated data* The function, $f(t)$ was fitted to each set of data using a valid non linear least squares method The estimated values of the λ_i A_i and their estimated standard deviations deduced from the variance covariance matrix of each fit were obtained Each set of data was simulated fifty times (with everything the same except the random numbers employed to simulate the error) and analysed fifty times By this means the variability and bias of both the estimates of the parameters and the estimates of their standard deviations were studied

The computer programmes were written in Algol and run on an English Electric KDF 9 computer When this work was commenced the University

Table 2

Average standard deviations of λ_i as per cent of the true λ_i — These standard deviations are the means of those derived from the variance/covariance matrix at each fit

Ratio of rate constants λ_1/λ_2	Ratio of amplitudes A_1/A_2	Error in data	Number of data points: 11 — Equal spacing λ_1	λ_2	11 — Log equal spacing λ_1	λ_2	31 — Equal spacing λ_1	λ_2	31 — Log equal spacing λ_1	λ_2
10/1	6/1	2%	2 6	4 8	2 9	6 5	1 8	3 1	1 8	5 1
		5%	6 5	12 1	7 8	17 3	4 5	7 8	4 5	12 7
		10%	13 2	23 0	15 2	36 6	9 7	15 9	9 3	26 9
10/1	4/1	2%	3 1	2 7	3 1	3 6	2 1	1 8	2 0	2 9
		5%	7 6	6 9	8 2	9 6	5 3	4 4	4 9	7 4
		10	15 4	12 9	15 9	18 5	11 6	8 9	10 3	15 4
10/1	2/1	2%	5 0	1 6	4 8	2 3	3 2	1 0	2 8	1 7
		5	12 4	4 1	11 9	5 8	8 3	2 5	6 9	4 2
		10%	37 8	7 7	23 6	11 1	16 7	5 1	14 5	9 0
10/1	1/1	2%		*		*	5 5	0 7	4 5	1 2
		5%		*		*	14 4	1 9	11 1	3 1
		10%		*		*	34 3	3 9	23 4	6 7
6/1	10/1	1		*	5 4	62 7	*		*	
		2%	4 8	36 5		**	3 2	25 5	3 7	36 6
		5		**		**	7 8	67 3	**	
6/1	4/1	1%		*		*	*		1 3	2 6
		5	8 7	13 2	12 7	23 1	6 0	8 5	6 7	13 3
		10	18 4	25 3		**	13 5	17 3	13 0	26 7
6/1	2/1	2%	4 8	2 4	5 2	3 2	3 2	1 6	3 3	3 5
		5	11 6	6 2	13 7	8 6	8 1	3 8	8 1	6 3
		10%	22 5	11 7	28 0	20 1			17 2	13 6
6/1	1/1	2		*		*	5 1	10 2	5 0	1 7
		5		*		*	13 1	2 6	12 3	4 4
		10		*		*	**		26 6	9 5
4/1	10/1	0 5	1 8	14 5	4 8	54 3	*		1 5	14 1
		1	3 5	30 3		**	2 5	20 1	2 9	27 8
		2		**		**	4 8	41 7	6 2	[illegible]
4/1	6/1	1	2 9	11 6	6 7	37 0	2 1	8 1	2 4	11 3
		2	5 9	24 5		**	4 0	16 6	4 8	22 3
		5		**		**	10 6	40 0	**	
4/1	2/1	2	5 9	4 3	8 4	7 [illegible]	4 0	3 0	4 5	4 5
		5	14 3	10 7		**	10 4	7 6	11 6	11 7
		10		**		**	22 8	17 1	**	
4/1	1/1	2		*		*	5 7	1 8	6 2	2 7
		5		*		*	14 4	4 7	15 2	7 0
		10%		*		*	33 8	12 5	**	
2/1	10/1	0 5%		**		**	4 6	28 8	**	
2/1	6/1	0 5		**		**	3 5	17 4	4 7	22 2
2/1	4/1	0 5%		**		**	3 4	11 0	4 4	14 1
		1		**		**	7 2	22 0	**	
2/1	1/1	0 5%		*		*	4 2	2 7	5 1	3 8
		1%		*		*	8 3	6 1	9 9	7 8
		2%		*		*	16 8	12 1	**	

[illegible]ulated ** C[illegible] [illegible]t obtained

Table 3

Average standard deviations of λ_i as per cent of true λ_i — These standard deviations are the means of those derived from the variance/covariance matrix at each fit

Ratio of rate constants λ_2/λ_1	Ratio of amplitudes A_1/A_2	Error in data	Number of data points: 11, Equal spacing λ_1	λ_2	11, Log equal spacing λ_1	λ_2	31, Equal spacing λ_1	λ_2	31, Log equal spacing λ_1	λ_2
10/1	6/1	2	2 2	3 9	1 1	5 9	1 6	2 5	0 8	4 0
		5	5 2	9 9	3 1	15 5	3 8	6 3	1 9	10 1
		10	10 4	19 0	6 0	30 6	8 2	13 2	4 0	20 8
10/1	4/1	2	2 4	2 7	1 2	4 1	1 9	1 7	0 8	2 8
		5	6 0	6 9	3 4	10 4	4 7	4 4	2 1	6 8
		10	11 8	13 0	6 5	20 2	10 1	8 9	4 4	14 3
10/1	2/1	2	3 1	2 0	1 8	3 1	2 6	1 2	1 1	2 0
		5	7 7	5 3	4 8	7 9	6 4	3 2	2 8	4 9
		10	14 7	10 0	9 2	15 3	13 0	6 4	6 0	10 3
10/1	1/1	2		*		*	3 7	1 1	1 9	1 7
		5				*	9 3	2 8	4 6	4 1
		10					19 9	5 9	9 6	8 8
6/1	10/1	1		*	4 8	49 1				*
		2	2 9	33 5			1 9	22 6	3 0	31 2
		5		**		**	4 5	52 5		**
6/1	4/1	1		*					0 7	3 0
		5	5 7	15 0	6 3	26 4	3 9	9 9	3 7	15 1
		10	11 7	28 7			8 4	20 3	6 9	28 1
6/1	2/1	2	3 1	3 4	2 6	5 1	2 2	2 2	1 3	3 5
		5	7 6	8 8	6 8	13 4	5 5	5 6	4 4	8 6
		10	15 3	16 7	14 2	28 2			9 0	17 9
6/1	1/1	2		*			3 3	1 7	2 7	2 7
		5		*			8 4	4 4	6 6	6 6
		10				*		*	14 3	14 2
4/1	10/1	0 5	1 7	19 0	5 9	59 8			1 8	17 5
		1	3 3	3C 3			2 3	26 3	3 4	3ɔ 1
		2				*	4 4	49 1	7 2	73 4
4/1	6/1	1	2 4	16 2	6 9	42 5	1 6	11 0	2 5	15 1
		2	4 5	31 1			3 0	21 5	4 8	29 3
		5					7 5	52 6		*
4/1	2/1	2	3 9	7 5	€5	13 5	2 5	5 1	3 6	7 6
		5	9 3	17 6			6 3	12 €	9 0	18 6
		10				*	13 2	25 1		**
4/1	1/1	2					3 5	3 2	4 8	5 0
		5					9 3	8 8	12 2	12 5
		10					20 3	17 4		
2/1	10/1	0 5					11 5	11 6		*
2/1	6/1	0 5				*	7 9	48 5	11 3	67 9
2/1	4/1	0 5				*	7 5	30 9	10 3	41 2
		1				*	14 6	€0 3		
1	1 1	0 5					8 5	8 8	11 8	11 9
		1					17 5	18 2	22 3	22 5
		2					30 7	32 0		

* The combination of conditions was not simulated ** Convergence not obtained

Table 2

Average standard deviations of λ_i as per cent of the true λ_i — These standard deviations are the means of those derived from the variance/covariance matrix at each fit

Ratio of rate constants λ_1/λ_2	Ratio of amplitudes N_1/N_2	Error in data	11: Equal spacing λ_1	11: Equal spacing λ_2	11: Log equal spacing λ_1	11: Log equal spacing λ_2	31: Equal spacing λ_1	31: Equal spacing λ_2	31: Log equal spacing λ_1	31: Log equal spacing λ_2
10/1	6/1	2%	2.6	4.8	2.9	6.5	1.8	3.1	1.8	5.1
		5%	6.5	12.1	7.8	17.3	4.5	7.8	4.5	12.7
		10%	13.2	23.0	15.2	36.6	9.7	15.9	9.3	26.9
10/1	4/1	2%	3.1	2.7	3.1	3.6	2.1	1.8	2.0	2.9
		5%	7.6	6.9	8.2	9.6	5.3	4.4	4.9	7.4
		10%	15.4	12.9	15.9	18.5	11.6	8.9	10.3	15.4
10/1	2/1	2%	5.0	1.6	4.8	2.3	3.2	1.0	2.8	1.7
		5%	12.4	4.1	11.9	5.8	8.3	2.5	6.9	4.2
		10%	37.8	7.7	23.6	11.1	16.7	5.1	14.5	9.0
10/1	1/1	2	*		*		5.5	0.7	4.5	1.2
		5%	*		*		14.4	1.9	11.1	3.1
		10%	*		*		34.3	3.9	23.4	6.7
6/1	10/1	1	*		5.4	62.7	*		*	
		2%	4.8	36.5	**		3.2	25.5	3.7	36.6
		5%	**		**		7.8	67.3	**	
6/1	4/1	1%	*		*		*		1.3	2.6
		5%	8.7	13.2	12.7	23.1	6.0	8.5	6.7	13.3
		10	18.4	25.3	**		13.5	17.3	13.0	26.7
6/1	2/1	2%	4.8	2.4	5.2	3.2	3.2	1.6	3.3	3.5
		5	11.6	6.2	13.7	8.6	8.1	3.8	8.1	6.3
		10%	22.5	11.7	28.0	20.1			17.2	13.6
6/1	1/1	2%	*		*		5.1	10.2	5.0	1.7
		5%	*		*		13.1	2.6	12.3	4.4
		10	*		*		**		26.6	9.5
4/1	10/1	0.5	1.8	14.5	4.8	54.3	*		1.5	14.1
		1	3.5	30.3	**		2.5	20.1	2.9	27.8
		2	**		**		4.8	41.7	6.2	58.6
4/1	6/1	1	2.9	11.6	6.7	37.0	2.1	8.1	2.4	11.3
		2%	5.9	24.5	**		4.0	16.6	4.8	22.3
		[illegible]	**		**		10.6	40.0	**	
4/1	2/1	2	5.9	4.3	8.4	7.5	4.0	3.0	4.5	4.5
		5%	14.3	10.7	**		10.4	7.6	11.6	11.7
		10	**		**		22.8	17.1	**	
4/1	1/1	2%	*		*		5.7	1.8	6.2	2.7
		5%	*		*		14.4	4.7	15.2	7.0
		10%	*		*		33.8	12.5	**	
2/1	10/1	0.5%	**		**		4.6	28.8	**	
2/1	6/1	0.5%	**		**		3.5	17.4	4.7	22.2
2/1	4/1	0.5%	**		**		3.4	11.0	4.4	14.1
		1%	**		**		7.2	22.0	**	
2/1	1/1	0.5%	*		*		4.2	2.7	5.1	3.8
		1%	*		*		8.3	6.1	9.9	7.8
		2	*		*		16.8	12.1	**	

* This combination of conditions was not simulated ** Convergence not obtained

Table 3

Average standard deviations of λ_i as per cent of true λ_i — These standard deviations are the means of those derived from the variance/covariance matrix at each fit

Ratio of rate constants λ_1/λ_2	Ratio of amplitudes A_1/A_2	Error in data	Number of data points							
			11				31			
			Equal spacing		Log-equal spacing		Equal spacing		Log equal spacing	
			λ_1	λ_2	λ_1	λ_2	λ_1	λ_2	λ_1	λ_2
10/1	6/1	2	2.2	3.9	1.1	5.9	1.6	2.5	0.8	4.0
		5	5.2	9.9	3.1	15.5	3.8	6.3	1.9	10.1
		10	10.4	19.0	6.0	30.6	8.2	13.2	4.0	20.8
10/1	4/1	2	2.4	2.7	1.2	4.1	1.9	1.7	0.8	2.8
		5	6.0	6.9	3.4	10.4	4.7	4.4	2.1	6.8
		10	11.8	13.0	6.5	20.2	10.1	8.9	4.4	14.3
10/1	2/1	2	3.1	2.0	1.8	3.1	2.6	1.2	1.1	2.0
		5	7.7	5.3	4.8	7.9	6.4	3.2	2.8	4.9
		10	14.7	10.0	9.2	15.3	13.0	6.4	6.0	10.3
10/1	1/1	2	*		*		3.7	1.1	1.9	1.7
		5	*				9.3	2.8	4.6	4.1
		10	*		*		19.9	5.9	9.6	8.8
6/1	10/1	1	*		4.8	49.1			*	
		2	2.9	33.5	*		1.9	22.6	3.0	31.2
		5	**				4.5	57.5	*	
6/1	4/1	1	*						0.7	3.0
		5	5.7	15.0	6.3	26.4	3.9	9.9	3.7	15.1
		10	11.7	28.7			8.4	20.3	6.9	28.1
6/1	2/1	2	3.1	3.4	2.6	5.1	2.2	2.2	1.3	3.5
			7.6	8.8	6.8	13.4	5.5	5.6	4.4	8.6
		10	15.3	16.7	14.2	28.2			9.0	17.9
6/1	1/1	2	*		*		3.3	1.7	2.7	2.7
		5	*				8.4	4.4	6.6	6.6
		10			*				14.3	14.2
4/1	10/1	0.5	1.7	19.0	5.9	59.8	*		1.8	17.5
		1	3.3	36.3	*		2.3	26.3	3.4	35.1
		2			*		4.4	49.1	7.2	73.4
4/1	6/1	1	2.4	16.2	6.9	[illegible]	1.6	11.0	2.5	15.1
		2	4.5	31.1	*		3.0	21.5	4.8	29.3
		5	*		**		7.5	52.6		
4/1	2/1	2	3.9	7.5	6.5	[illegible]	2.5	5.1	3.6	7.6
		5	9.3	[illegible]			6.3	12.6	9.0	18.6
		10			*		[illegible]	25.1		
4/1	1/1	2	*				3.5	3.2	4.8	5.0
		5					9.3	8.8	12.2	12.5
		10					20.3	17.4	*	
2/1	10/1	0.5	*				11.5	11.6		
2/1	6/1	0.5					7.9	48.5	11.3	67.9
2/1	4/1	0.5			**		7.5	30.9	10.3	41.2
		1	**				14.6	60.3	*	
2/1	1/1	0.5			*		8.5	8.8	11.8	11.9
		1					17.5	18.2	22.3	22.5
		2	*				30.7	32.0	*	

* The combination of conditions was not simulated ** Convergence not obtained

of Sydney did not possess an IBM 7090, or a Fortran compiler, and thus none of the well known fitting programmes, e.g. BERMAN, SHAHN & WEISS (1962) could be used.

Results

1. *Convergence of the iterations.* The maximum amount of error in the data that permitted convergence of this simple numerical technique was as shown in Table 1. In each case the true parameter values (used in generating the relevant data) were used as starting values for the iteration. From the point of view of starting values, these results thus represent the most favourable situation it is possible to achieve.

No special techniques were used to help the convergence. Each set of data was simulated fifty times, and a failure to converge for at least one set was regarded as meaning that convergence was not obtained for those data. In these regards the results are somewhat less favourable than might be obtained in practice.

Failure of convergence was judged to have occurred if, in the process of calculation, a number exceeded the machine limit ($\sim 10^{38}$) (this was almost always the case) or, rarely, if the change in parameter values was not less than 10^{-4} and the change in variance not less than 10^{-6} after twenty iterations. The parameter values were in the range 0.01 to 1.00.

2. *Error in the λ_i as a function of error in data and number of data points.* Table 2 shows the average error (throughout this paper error means percentage error) in λ_1 and λ_2 as a function of magnitude of error in the data, and number of data points, for normally distributed error. One result is obvious: 31 points give a lower error than 11 points for the same data error.

The lesser rate constant, λ_2, which largely determines the tail of the data, has more error than the greater constant, λ_1, if $N_1/N_2 > 4$ and $\lambda_1/\lambda_2 \geq 4$, and if the data are spaced equally in log time. The same holds for equally spaced data except that if $\lambda_1/\lambda_2 = 10$ and $N_1/N_2 = 4$, then the error in λ_2 is the least. If $\lambda_1/\lambda_2 \geq 4$ and $N_1/N_2 \leq 2$, then the error in λ_2 is lower than in λ_1, except that for $\lambda_1/\lambda_2 = 4$ and $N_1/N_2 = 2$, the errors are equal. For $\lambda_1/\lambda_2 = 2$, the error in λ_2 is lower for $N_1/N_2 = 1$ only. These statements apply to the studies with 31 points and the error referred to is the percentage error, as is always the case in this paper.

The same results were observed in studies with eleven points except that for data spaced equally in log time if $\lambda_1/\lambda_2 = 4$ and $N_1/N_2 = 2$, then the error in λ_2 is the lesser.

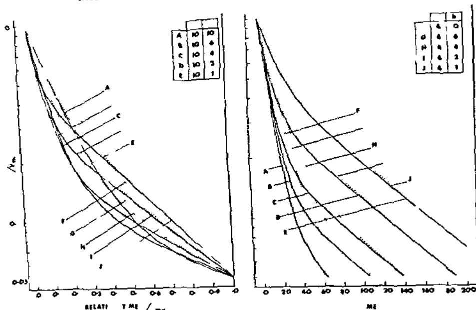


Fig 1 Sums of two exponentials having rate constants of ratio 10 and 6 The amplitude ratios are 10 6 4 2 and 1 A sum is terminated when it has declined to 5 of its initial value Each curve is plotted twice on the left both magnitude and time are normalised on the right the magnitude alone is normalised

The percent error in λ_1 was only sometimes lessened by employing log equal spacing of the data while the percent error in λ_2 was always increased

3 *Error in N_1 as a function of error in data and number of data points* The average errors in N_1 and N_2 as a function of magnitude of error in the data and number of data points for normally distributed error are shown in Table 3

With 31 points and log equally spaced data the percent error in N_2 is equal to that in N_1 when $N_1/N_2 = 1$ irrespective of λ_1/λ_2 and is greater than that in N_1 for all other values of N_1/N_2 The same holds for 11 points

For equally spaced data if $N_1/N_2 \geqslant \lambda_1/\lambda_2$ then the percent error in N_2 is the greater The errors are about equal for $\lambda_1/\lambda_2 = 10$ and $N_1/N_2 = 4$ $\lambda_1/\lambda_2 = 6$ and $N_1/N_2 = 2$ $\lambda_1/\lambda_2 = 4$ or 2 and $N_1/N_2 = 1$ For each of these values of λ_1/λ_2 if N_1/N_2 exceeds the value quoted then the percent error in N_2 is the greater otherwise it is the lesser

For log equal spacing the absolute errors in the N_i are approximately equal

For $\lambda_1/\lambda_2 \geqslant 6$ the log equal spacing (i e crowding the points near the

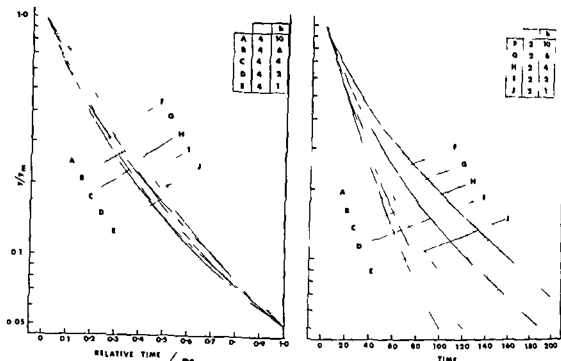


Fig 2 Sums of two exponentials having rate constants of ratio 4 and 2 The amplitude ratios are 10 6 4 2 and 1 A sum is terminated when it has declined to 5 of its initial value Each curve is plotted twice on the left both magnitude and time are normalised on the right the magnitude alone is normalised

beginning of the data) always improved the per cent error in N_1, over that obtained in equally spaced data For $\lambda_1/\lambda_2 \leq 4$ the opposite was true

Discussion

The tracer activity curve in any steady state two compartment open system can be described by a sum of two exponential terms The relationships between the transfer rates and compartment sizes, on the one hand, and the rate constants (λ_i) and amplitudes (N_i), on the other hand, are expressible by simple algebraic equations The form of the equations depends on the configuration of the system, and these equations can be used to transform information on the errors obtained in λ_i and N_i to information about the associated errors in the transfer rates and compartment sizes By this means this error information can be applied to a range of biological problems, mainly tracer studies in biochemistry and physiology

Within the conditions here investigated convergence is readily obtained by this simple numerical method if the ratio of λ_1 to λ_2 is not less than about

four For lower ratios (i e rate constants more nearly equal) a very good experiment is necessary that is, the standard deviation in each data point should be about 1 % In practice since the best starting values for the iteration are of course unknown convergence may be difficult to obtain even when these requirements are satisfied However the employment of various techniques to help convergence and trial of various starting values would improve the situation over that shown in Table 1

For any desired error in λ_i or A_i the allowable error in the data may be found from Tables 2 and 3 As the data error increases the parameter error increases proportionately For the same error in each point taking more points results in a smaller parameter error The variation of error in the λ_i and A_i depends on the spacing of the data points and the ratios λ_1/λ and A_1/A The parameter errors could be reduced by collecting data extending further in time as well as by lowering the error in each point or taking more points over the same time interval The present study, however was to examine the situation where for experimental reasons the data could not be extended further in time

The conclusions of this paper apply to any two compartment system from which data has been collected until $f(t) = qf(0)$, $q = 0\,05$ in one of the compartments, and for which $\lambda_1 > \lambda_2$ implies $A_1 \geqslant A_2$ The results do not depend on the absolute magnitudes of the A_i or λ_i In practice if q is larger then the analysis is more difficult the errors in A_i and λ_i will be greater and the situation is worse in other respects If q is smaller, i e the data are sampled for a longer time the results will be better If more data points are taken the results will also be better The results quoted herein can thus afford a guide in evaluating other situations If three compartments are being studied then the results would be the best that one could possibly achieve for the errors in four of the six parameters

SUMMARY

The effect of error in radiotracer data on the accuracy of derived parameters in two-compartment systems was studied Computer simulation was employed to produce data with error of different magnitude for each of several values of rate constant and amplitude The data were arranged to simulate experimental situations and analysed by non linear least squares For a given error in the data the calculated errors in the rate constants and amplitudes were defined in terms of their ratios and the number and spacing of the data points

ZUSAMMENFASSUNG

Der Einfluss der bei der Analyse mit radioaktiven Tragern entstandenen Datafehler auf die Genauigkeit der derivierten Parameter wurde studiert Bei Simulation mit einer Datenverarbeitungsmaschine wurden Datafehler verschiedener Grosse fur jeden von mehreren

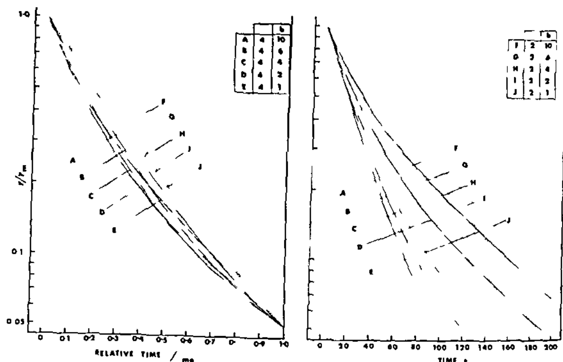


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Zahlwerten der Geschwindigkeitskonstanten und Amplituden produziert Die Daten sollten experimentelle Bedingungen simulieren und wurden mit der Methode nicht linearer Mindest Quadraten analysiert Fur einen bestimmten Datafehler wurden die berechneten Fehler in Geschwindigkeitskonstanten und Amplituden als Funktionen der Verhaltniszahlen der Konstanten und Amplituden sowie der Anzahl und Abstande der Datapunkte ausgedruckt

RÉSUMÉ

L auteur a étudié l effet d erreurs de mesures de radioactivité de traceurs sur l exactitude des paramètres calculés à partir de ces mesures Il a utilisé la simulation sur ordinateur pour obtenir des mesures entachées d erreurs de différentes grandeurs pour chaque des différentes valeurs des constantes de vitesse et des amplitudes Il a combiné ces mesures de façon a simuler des situations expérimentales et les a analysées par la méthode non linéaire des moindres carrés Pour une erreur donnée de la mesure il a calculé les erreurs sur les constantes de vitesse et sur les amplitudes pour différentes valeurs de leurs rapports et pour différents nombres et différents espacements des points de mesures

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FROM THE DEPARTMENT OF GYNECOLOGY ROSWELL PARK MEMORIAL INSTITUTE AND STATE UNIVERSITY OF NEW YORK AT BUFFALO SCHOOL OF MEDICINE BUFFALO U S A

INCIDENCE OF SECOND CANCERS AFTER RADON SEED THERAPY FOR CERVIX CANCER

by

JOHN GRAHAM and PAUL BURSTEIN

Addendum by S S KUROHARA

Radiotherapy is the standard treatment for invasive cancer of the uterine cervix Nowadays intracavitary radium plus external roentgen is usually employed A generation ago interstitial radon seeds were widely used instead of or in conjunction with intracavitary radiation Because of some late complications and second cancers in radon seed treated cases we reviewed all cases of primary cervical cancer treated in our hospital from 1927—1953 We found that the frequency of other cancer formation and of radiation complications was influenced by the use of seeds

In Table 1 are indicated the number of cases treated in five periods from 1927 to 1953 The method of treatment the number surviving and the number of second cancers is shown in 5 year increments A minimum follow up of 10 years is available for all The usual treatment was a course of external roentgen therapy directed toward the mid pelvis given through 4 or 6 portals anterior posterior and lateral The central pelvic dose was given with about 1 000 R per week It usually totalled 3 000 to 5 000 R and after an interval of about two weeks 10 to 12 gold radon seeds 1 mCi/seed were introduced in the cervix

Submitted for publication 2 February 1968

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Table 1

Time of treatment survival rates and second cancers

Treatment period	Number of cases Treated		2nd	Ca	0—5 years 2nd	Ca	5 year survival		6—10 years 2nd	Ca
	c̄	s̄	c̄ x	s̄ x	c̄ xx	s̄ xx	c̄	s̄	c̄ xx	s xx
1927—1931	320	71	12 4 %	1 1 %	0	0	72 22 %	12 17 %	2	0
1932—1936	786	56	19 2 %	5 9 %	1	1	253 32 %	27 48	5	2
1937—1941	802	171	17 2 %	12 7 %	3	2	277 34 %	53 31 %	3	1
1912—1946	89	834	5 6 %	59 7 %	1	11	29 33 %	364 44 %	1	16
1947—1953	72	1 014	1 1 %	56 6 %	0	13	32 44 %	440 43 %	1	14
All	2 069	2 146	54 2 7 %	133 6 2 %	5 0 8 %	27 3 %	663 32 %	896 42 %	12 2 3	33 4 6 %

c̄ with radon seeds s̄ without radon seeds x percentage of 2nd cancers calculated on base of treated cases listed in previous column xx percentage of 2nd cancers calculated on basis of treated cases listed in following column

An alternate method of completing the treatment was to apply intracavitary radium to bring the total dose at point A to 7 500 to 8 500 R Favorable stage I cases were treated by intracavitary radium alone Some patients who had a very good response to the roentgen with healing of the upper vagina and cervix had no seeds or radium Patients with a large, bulky lesion after roentgen therapy were more likely to be given intracavitary radium than seeds Others with progressive disease after the roentgen were given no further treatment The overall character of the material in the two groups is rather similar in terms of age at time of treatment and clinical stage (see Table 2) The selection of patients for a particular form of treatment varied from time to time as can be seen from Table 1

Two experienced gynecologists each reviewed all of the hospital records in a uniform manner The data are summarized in Tables 1 3 and 4 The follow up

Table 1 *(cont)*

10-year survival		11—15 years 2nd	Ca	15-year survival		16—20 years 2nd	Ca	20 year survival		21+years 2nd	Ca
c	s	c xx	s xx	c̄	s	c̄ xx	s̄ xx	c̄	s̄	c̄ x	s̄ x
51	8	2	0	43	5	1	0	37	4	7	1
18₅	19	2	1	149	16	6	1	96	13	5	0
227	4₅	2	4	178	37	4	2	14?	29	5	3
						11	3	275	46	17	4
						4 °	6 5 /			6 °	9 /
23	29?	1	18	13	231	2	11			0	3
		all 7	23	283	289						
		1 8	8								
31	347	0	22			0	7				
51	711	7	45	383	289	13	21	275	46	17	7

was complete in 98 % of all cases The total number of cases treated with seeds and without seeds are approximately the same i e 2 069 and 2 146 The survival rate for the non seed cases is better than for those treated with seeds i e 42 % versus 32 % The difference probably is related to selection and time of treatment The number surviving in each group through 15 years is roughly the same There are more seed cases living at 20 years because more cases were treated with seeds in the early years

The major radiation complications occurred in non seed cases more than twice as frequently as in seed cases in the first 15 years This is probably explained by larger doses of total radiation given in the non seed group The complications in the 16th to 20th year were about the same in both groups and the complication after the 21st year was in a seed case

Second primary cancers are listed in Table 4 Adenocarcinomas of the uterine

body were accepted as second cancer if the cervical lesion was squamous These occurred with about the same frequency in both groups There were six uterine sarcomas in the non seed group and two in the seed cases There were more cancers in non seed cases of almost all sites Exceptions were adenocarcinoma of the corpus, carcinoma of the vagina and leukemia Leukemia occurred in five seed cases and in two non seed cases In seed cases this is ten times the incidence in the general population Of the five cases, three were lymphatic, one myelogenous and one unknown It is remarkable that all 18 of the skin cancers occurred in the non seed group Second cancers occur more frequently in non seed cases at all intervals after treatment

The non seed cases received a larger dose of radiation from both roentgen and radium than the seed cases All of the exposure occurred within a brief period of a few weeks while treatment was given The seed cases tended to have a lower integral dose Perhaps of more importance is the prolonged low intensity radiation that they received from the retained seeds which contain radium D, the residue of radon (GRAHAM, GRAHAM, SOTTO & BAILY 1960) Radium D has a half life of 18 years It emits beta rays of 1 17 MeV that excite the gold to generate a continuous spectrum of roentgen radiation with peaks at 70 and 167 keV Seed cases are found to retain seeds in the region of the cervix for 20 or more years and the retained seeds usually have some residual, measurable radioactivity The total dose from radium D is in the range of 100 to 300 rad

From the present data it is impossible to determine whether the second cancers are more or less frequent than normal in these two groups BELONOSCHKIN reported from Sweden that they found an incidence of 4 6 % (61 in 1 330) second cancers in cancer of the cervix patients six years or more after treatment Their follow up ranged from 10 to 40 years Their cases were treated with intracavitary radium and none with seeds Comparable figures in our series are 12 % (106 of 896) in the non seed cases and 7 4 % (49 of 663) in the seed cases

Radon seeds provide effective irradiation for cervical cancer The cure and complication rates are comparable to those using other forms of treatment The higher frequency of leukemia in seed cases is not unexpected in view of the protracted low intensity exposure The remarkable finding is that other cancers occurred less than half as frequently in the seed cases This cannot be explained by selection, for stage of disease age, etc are roughly the same It is likely that the radon seeds exerted this effect The gold is probably inert One explanation is that prolonged low intensity radiation of radium D has a beneficial effect Perhaps it stimulates the defense mechanism to oppose the development of new cancer

This concept is contrary to mortality rates in radiologists who are assumed to be exposed to radiation more than others (SELTSER & SARTWELL 1964) They

Table 2

Distribution of cases by age and clinical stage

Age	No seeds	Seeds
—29	3	3
30—39	16	17
40—49	29	30
50—59	27	30
60—69	18	15
70 or more	7	5
Clinical stage		
I	21	13
II	33	34
III	29	36
IV	17	17

Table 3

Major radiation complications

	Time after treatment of cervical cancer											
	0—5 years		6—10 years		11—15 years		16—20 years		21+ years		All	
	c	s	c	s	c	s	c	s	c	s	c	s
Bladder fistula	4	[illegible]	1			3	1				6	5
Rectal fistula	3	9		4		4	1	1	1		5	18
Recto-sigmoid stricture		1	1			2		1			1	5
Vesico-sigmoid vaginal fistula				1								1
Urethro-vaginal fistula		1										1
Ileo-vaginal fistula		1										1
Ileal perforation		1										1
Totals	7	16	2	5	—	9	2	2	1	—	1[illegible]	3[illegible]

have a higher death rate from leukemia (19 observed versus 8 expected) and other cancers (135 observed versus 87 expected) than ophthalmologists and otolaryngologists. The character of irradiation and timing of exposure is quite different in our series and in radiologists. The carcinogenic property of ionizing radiation is well known (LITTLE 1966). Its stimulant effect on defense mechanisms is less familiar. Locally applied radiation will increase antibody production (GRAHAM & LESKOWITZ 19[illegible]6; GRAHAM, GRAHAM, NERI & WRIGHT 19[illegible]6) and mast cell concentration in the exposed area (GRAHAM & GRAHAM 1966).

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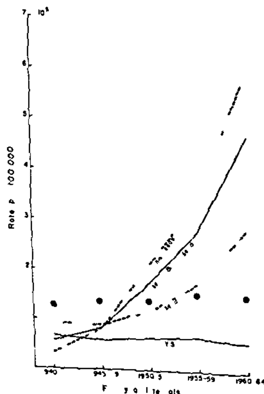
Addendum in proofs

by

S S KUROHARA

Second cancer incidence rates were calculated for cervical cancer patients treated with seeds alone or in combination with roentgen irradiation and for those treated with radium alone roentgen irradiation or both These rates were based on the number of patients still alive (at risk to develop second cancers) during 5 year intervals beginning at 1940 and ending at 1964

Since the age of occurrence of second primaries in these patients was 40 or more years the New York State (exclusive of the city) rates for normal females for these age ranges were calculated from published data (FERBIER et coll 1962) The incidence rates of second cancer rise in both treatment groups from 1940 through 1964 are given in the figure below These rates during 1940 to 1944 are very close to the normal one The rise is significantly higher for the non-seed group than for the seed group



Second cancer incidence rates plotted against 5 year chronologic time intervals Cancer incidence rates for the normal female population over 40 years of age in New York State (exclusive of the city) are shown for these time intervals The solid circles indicate New York State incidence rates corrected for age distribution of patients at risk The rate of radon seed radiotherapy is significantly lower than that for non seed radiotherapy at time interval 1950—1964 ($P < 0.001$)

Table 4

Incidence and type of second cancers occurring after radon seed therapy for cervix cancer

	Time of occurrence after first treatment of cervix cancer											
	0—5 years		6—10 years		11—15 years		16—20 years		21+ years		All	
	$\bar{c}$	$\bar{s}$	$\bar{c}$	$\bar{s}$	$\bar{c}$	$\bar{s}$	$\bar{c}$	$\bar{s}$	$\bar{c}$	s	c	s
Adenocarcinoma of uterine corpus	0	1	3	3	2	3	1	0	3	1	9	8
Uterine sarcoma & mixed	1	0	0	4	0	1	1	1	0	0	2	6
Carcinoma vulva	0	2	0	0	0	0	1	0	1	0	0	4
Carcinoma vagina	0	0	0	1	1	1	1	0	2	0	4	2
Carcinoma pelvis			0	1							0	1
Carcinoma ovary	0	1	0	4	1	5	1	0	0	1	?	11
Carcinoma breast	0	5	4	6	2	10	3	1	2	3	11	25
Carcinoma bladder	2	0	1	0	1	5	2	3	0	0	6	8
Carcinoma colon and rectum	0	6	2	3	0	5	3	5	4	0	9	19
Leukemia	1	0	2	1	0	1	0	0	2	0	5	2
Myeloma			0	1							0	1
Lymphoma					0	1	0	1			0	2
Carcinoma kidney			0	1					1	0	1	1
Carcinoma lung	1	1	0	4	0	6	1	1	0	1	2	13
Carcinoma liver									1	0	1	0
Carcinoma larynx									1	0	1	0
Carcinoma esophagus									1	0	1	0
Carcinoma stomach			0	1	0	1	0	2			0	4
Sarcoma stomach					0	1					0	1
Carcinoma pancreas							0	1			0	1
Carcinoma tongue	0	1									0	1
Carcinoma mouth					0	1					0	1
Lymphosarcoma tonsil					0	1					0	1
Carcinoma thyroid									0	1	0	1
Carcinoma brain					0	1					0	1
Carcinoma skin	0	10	0	2	0	1	0	5			0	18
Melanoma			0	1							0	1
All	5	27	12	33	7	45	13	21	17	7	54	133

Animal studies show that low intensity total body irradiation may increase longevity (CARLSON, SCHEYER & JACKSON 1957, LORENZ, HOLLCROFT, MILLER et coll 1955) However, there is an associated increase in tumor formation We know of no animal studies where low intensity local radiation was given

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Graham R M and Graham J B Mast cells and cancer of the cervix Surg Gynec Obstet 123 (1966) 2

Little J B Environmental hazards Ionizing radiation New Engl J Med 275 (1966) 929

Lorenz F Hollcroft J W Miller E et coll Long term effects of acute and chronic irradiation in mice I Survival and tumor incidence following chronic irradiation of 0 11 r per day J nat Cancer Inst 15 (1955) 1049

Seltser R and Sartwell E The effect of occupational exposure to radiation on the mortality of physicians J Amer med Ass 190 (1964) 1046

SUMMARY

Study of patients with carcinoma of the cervix first seen in the period 1927—1953. Radiotherapy including radon seeds was given to 2 069 patients and without seeds to 2 146 patients. All were followed up for periods between 10 and 35 years. Age, stage distribution and survival rates in the two groups were about the same. The frequency of secondary cancer in the non-seed cases was twice that in the radon seed group. The difference is probably significant for it was found throughout the period of observation. The reason for the difference is not clear.

ZUSAMMENFASSUNG

Es wird über eine Studie an Patienten mit Cervixkarzinom berichtet, die erstens während der Periode 1927—1953 zur Untersuchung kamen. Radiotherapie einschliesslich Radon samen wurde an 2 069 Patienten gegeben und Radiotherapie ohne Samen an 2 146 Patienten. Alle wurden über Perioden zwischen 10 und 35 Jahren beobachtet. Altersverteilung, Tumorstadium und Überlebungsrate waren dieselben für die beiden Gruppen. Die Frequenz von Sekundarkanzer war doppelt so gross in der Gruppe die keine Radonsamen erhielt im Vergleich zur Radongruppe. Diese Differenz wurde während der ganzen Periode beobachtet und muss wahrscheinlich als signifikant betrachtet werden, obwohl die Ursache dieser Differentz nicht klar ist.

RÉSUMÉ

Les auteurs ont étudié le cancer du col de l'uterus chez des malades vues pour la première fois au cours de la période allant de 1927 à 1953. Le traitement de ces malades était radiothérapie comprenant l'implantation de grains de radon dans 2 069 cas et radiothérapie sans grains dans 2 146 cas. Les malades ont eté suivies pendant 10 à 35 ans. L'age, le stade, la distribution et le taux de survie étaient à peu près les mêmes dans les deux groupes. La frequence d'un cancer secondaire chez les malades qui n'avaient pas eu de grains de radon a été double de celle du groupe traité par les grains de radon. Cette différence est probablement significative car on la retrouve pour toute la période d'observation. La raison de cette différence n'est pas claire.

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FROM THE RESEARCH LABORATORY OF MEDICAL ELECTRONICS (DIRECTOR PROF HENRY WALLMAN), CHALMERS UNIVERSITY OF TECHNOLOGY, AND THE DEPARTMENT OF RADIOTHERAPY (DIRECTOR PROF MAGNUS STRANDQVIST) UNIVERISTY OF GOTHENBURG, SWEDEN

FIELD CONTROL IN ROENTGEN THERAPY WITH A 5 MeV LINEAR ACCELERATOR BY MEANS OF TELEVISION

by

ROLAND MALVEN, BENGT ROSENGREN and HENRY WALLMAN

Field control of direct roentgen irradiation from a 30 MeV betatron and direct gamma irradiation from a cobalt 60 unit were described in two previous publications (BENNER, ROSENGREN, WALLMAN & NETTELAND 1962 and MALVEN, ROSENGREN & WALLMAN 1965) The advantages of continuous and direct monitoring, especially in connection with the use of small fields, were pointed out in these articles The technical difficulties involved in obtaining adequate contrast and detail were also discussed

One of the therapeutically important advantages of high voltage radiation is the small difference in absorbtion between various tissues, this, however, necessarily implies low contrast The possibility of contrast enhancement afforded by television techniques, combined with the use of either gold as an indicator, or air as negative contrast, makes it possible to achieve satisfactory reproduction

Submitted for publication 8 August 1967



Fig 1 Correspondi g pa r of accel rator televis on image (a) and roentgenogram obtained with 125 kV (b) from a pat ent with bladder insufflated w th CO_2 (contrast level at *) Symphysis pub s (—→) hip jo nt (→→) Image (a) corresponds to area outl ned in (b)

In the most recent paper (MALVEN et coll 1963) this contrast enhancement was exemplified by photographs taken from a television monitor screen during treatment of a gynecologic carcinoma with metastases in the pelvic wall marked by gold indicators Other examples included insufflation of gas into the bladder for a brief localization preceding the treatment itself (which should be given with an empty bladder), and use of the air present in the upper respiratory tract for observation of the laryngeal or pharyngeal tumours during treatment

The technique was described in detail in the first paper (BENNER et coll) Mention was made in the second paper (MALVEN et coll) of the modifications arising from the use of a cobalt unit

In the present contribution the use of this technique in connection with therapy with a 5 MeV linear accelerator will be described

The radiation qualities with a gamma unit and a 5 MeV linear accelerator are therapeutically equivalent with a somewhat larger depth dose with the latter The penumbra is, however considerably smaller in the case of the linear accelerator, in view of the fact that the focus is about 4 mm in diameter whereas the radiation source in our cobalt unit is 20 mm × 20 mm

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Fig 1 Corresponding pair of accelerator television image (a) and roentgenogram obtained with 125 kV (b) from a patient with bladder insufflated with CO (contrast level at *) Symphysis pubis (⟶) hip joint (⟷) Image (a) corresponds to area outlined in (b)

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Fig 3 Corresponding accelerator television image (a) and roentgenogram (b) from a patient with laryngeal carcinoma Epiglottis (—›) introitus laryngis (×) vocal cord level (+—›) trachea (*)

approximately the same extent in the two images Definition is however less good in the accelerator television image although the anatomical details are sufficient to permit an orientation It is also apparent from the television image that the medulla is not being irradiated

A similar comparison was made in a case of laryngeal carcinoma as demonstrated in Fig 3

Conclusion

The amount of detail in the high voltage roentgen television image cannot of course be compared with that in conventional roentgen films owing to the lower contrast produced by the high energy radiation Another reason is that roentgenograms are usually obtained in projections selected in the manner most favourable from the diagnostic point of view On the other hand the megavolt roentgen television images are based upon projections determined by the location of the field of treatment, these in turn being determined by considerations of optimal dose distribution The megavolt



Fig 2 Corresponding pair of accelerator television image (a) and roentgenogram obtained with 125 kV (b) from a patient with tonsil tumour Filled teeth (—→) soft palate (+→) mandible (*)

in size Better definition but somewhat poorer contrast should therefore be obtained in television monitoring with a linear accelerator in place of a cobalt unit

The same technical equipment for field control in connection with these two therapeutic units was employed Definition was better with the linear accelerator, although the improvement was not so great as could have been expected from a comparison of the focus sizes The contrast was, as expected, somewhat poorer with the linear accelerator than with the cobalt unit

A bladder in which gas (carbon dioxide) was insufflated previous to treatment is well outlined in Fig 1a, an indicator roentgenogram (125 kV) of the same patient in the same projection, is reproduced in Fig 1b The negative contrast in the gas filled part of the bladder and in the rectum is satisfactory in the high voltage roentgen television image The definition and the contrast are of course considerably poorer than in the roentgen film

A corresponding pair of images from a patient with tonsil tumour treated with the linear accelerator are represented in Fig 2 The air is visible to



Fig. 3. Corresponding accelerator television image (a) and roentgenogram (b) from a patient with laryngeal carcinoma. Epiglottis (⟶), introitus laryngis (×), vocal cord level (+⟶), trachea ( ).

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images can, however, provide the radiation therapist with good localization of the field of treatment, and increasing experience in the interpretation of the appearances arising from the projections occurring in therapy will add considerably to their value

SUMMARY

A special system for field control in linear accelerator therapy is described and exemplified with treatments of the head neck, and pelvic regions

ZUSAMMENFASSUNG

Ein neues Feldkontrollsystem fur die Bestrahlung mit linearen Schleudern wird beschrieben und mit Beispielen fur die Behandlung von Kopf Hals und Becken illustriert

RÉSUMÉ

Les auteurs décrivent un systeme spécial de localisateur de champ pour le traitement par accélérateur linéaire et donnent des exemples de traitements des regions de la tete du cou et du bassin

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MALVEN R ROSENGREN B and WALLMAN H Field control of telecobalt therapy by gamma ray television Acta radiol Ther Phys Biol 3 (1965) 425

AUS DEM LABORATORIUM FÜR RÖNTGENTECHNIK DER MEDICORWERKE, BUDAPEST, UNGARN

RÖNTGENTECHNISCHE ALLGEMEINE THEORIE

von

L. CSEPINSZKY

Mehr als ein halbes Jahrhundert ist vergangen, seitdem die Röntgentechnik in der ärztlichen Praxis erfolgreich angewendet wird. Trotzdem ist auf diesem Gebiete der Technik noch keine zusammenfassende allgemeine Theorie bekanntgemacht worden, die sämtliche bisherigen Ergebnisse zusammenfassen, auf das erzielbare Ideal hinweisen und eine Vergleichsbasis für die verschiedenen technischen Lösungen schaffen würde. Der Verfasser hat seine Theorie — vorwiegend in ihren regelungstechnischen Beziehungen — bereits früher veröffentlicht (1964), jedoch ausschliesslich für technische Fachleute und nicht vor einem internationalen Forum. Diesen Mangeln möchte ich jetzt durch Veröffentlichung meiner Arbeit, ausführlicher als früher und vor dem internationalen Forum der röntgentechnisch interessierten Forscher abhelfen.

In den Jahren, die auf den zweiten Weltkrieg folgten, haben zahlreiche Forscher zum Ziele gesetzt, die praktischen und theoretischen Fragen in Verbindung mit der Weiterentwicklung der Röntgentechnik zu klären. So wird zum Beispiel — um nur einige von den vielen Forschern zu erwähnen — eine neue empirische Formel, die den Zusammenhang zwischen der Auf

Bei der Redaktion am 24. Oktober 1967 eingegangen

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von

L. CSEPINSZKY

Mehr als ein halbes Jahrhundert ist vergangen seitdem die Röntgentechnik in der ärztlichen Praxis erfolgreich angewendet wird. Trotzdem ist auf diesem Gebiete der Technik noch keine zusammenfassende allgemeine Theorie bekanntgemacht worden, die sämtliche bisherigen Ergebnisse zusammenfassen, auf das erzielbare Ideal hinweisen und eine Vergleichsbasis für die verschiedenen technischen Lösungen schaffen würde. Der Verfasser hat seine Theorie — vorwiegend in ihren regelungstechnischen Beziehungen — bereits früher veröffentlicht (1964), jedoch ausschliesslich für technische Fachleute und nicht vor einem internationalen Forum. Diesen Mängeln möchte ich jetzt durch Veröffentlichung meiner Arbeit ausführlicher als früher und vor dem internationalen Forum der röntgentechnisch interessierten Forscher abhelfen.

In den Jahren, die auf den zweiten Weltkrieg folgten, haben zahlreiche Forscher zum Ziele gesetzt, die praktischen und theoretischen Fragen in Verbindung mit der Weiterentwicklung der Röntgentechnik zu klären. So wird zum Beispiel — um nur einige von den vielen Forschern zu erwähnen — eine neue empirische Formel, die den Zusammenhang zwischen der Auf

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nahmespannung und mAs Wert (Milliamperseknnden Produkt) beschreibt, durch BIERMAN & BOLDINGH (1951) bewiesen und eingefuhrt STIEVE (1957), die fruheren Feststellungen von FRANKE weiterfuhrend, erforscht in seiner Arbeit, die die Dominanten behandelt, die Grosse des fur die Bildgestaltung wichtigen Bildausschnittes und seine Lage im Rahmen des ganzen Bildes bei verschiedenen Rontgenaufnahmen Anschliessend darin prufen WIDENMANN und Mitarbeiter (1962) die Wirkung der Form des Strahlenreliefs auf die mittlere Schwarzung KUNTKE (1957) macht aufnahmetechnisch wichtige Feststellungen in der Frage der Anderung der Strahlenausbeute der Rontgen rohre SHIGA (1963) macht Vorschlage zur Weiterentwicklung des in der Rontgenaufnahmetechnik seit langerer Zeit angewendeten Punktsystems und zur Standardisierung der Aufnahmetechnik

Die Arbeiten der beispielsweise aufgezahlten und auch der ubrigen, hier infolge Platzmangel nicht erwahnten namhaften Forscher werden dadurch charakterisiert, dass sie nicht bestrebt sind, die Ganze der Rontgentechnik betreffende, allgemein gultige Feststellungen zu machen, sondern sie befassen sich bezuglich der Vervollkommnung der Rontgentechnik nur mit einzelnen Teilproblemen und ihre Abhandlungen stutzen sich auf statistische und empirische Angaben

1 Grundgedanke der allgemeinen Theorie

Die Rontgentechnik wird in der Medizin hauptsachlich mit dem Ziel angewendet, um Informationen zu erhalten Die Informationen erhalten wir von stehenden, oder bewegten Bildern durch visuelle Betrachtung Trager des Informationsgehaltes sind die Helligkeitsunterschiede der einzelnen Bildpunkte (der einzelnen Flachenelemente) Die Beurteilung des Bildes, welche die Informationen vermittelt, ist immer subjektiv Die Charakterisierung des '*guten Rontgenbildes' kann nicht durch einen einzigen* Veranderlichen erfolgen, die Bildgute konnen wir nur aus verschiedenen, subjektiv festgelegten Gesichtspunkten interpretieren Nur aus diesem Standpunkt konnen wir einen *funktionellen Zusammenhang aufstellen zwischen einer die Bildgute* charakterisierende Grosse und den veranderlichen Parametern der Rontgentechnik

$$E = f_1 (x_1, x_2, \quad x_n) \tag{1}$$

wo E die Bildgute charakterisierende Grosse, und $x_1, x_2, \quad x_n$ die Veranderlichen der Rontgentechnik sind Nun besteht das Problem darin, dass wir diejenigen ausgezeichneten Werte $x_{1,0}, x_{2,0}, \quad x_{n,0}$ der Veranderlichen $x_1, x_2, \quad x_n$ suchen, bei denen das subjektiv gewahlte E auf einer

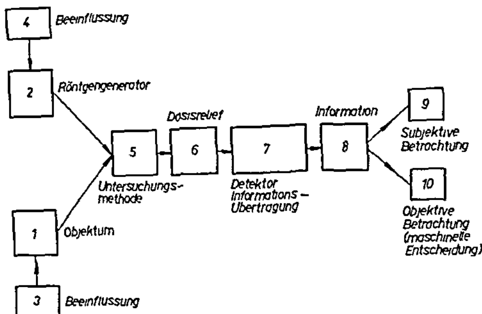


Abb. 1. Schema der Informationsgewinnung in der Röntgentechnik

ebenfalls subjektiv festgelegten Skala irgendeinen für uns günstigen Wert, z. B. in gewisser Hinsicht das Optimum aufnimmt.

Wir sind der Meinung, dass für eine Theorie der Bildgestaltung, welche für die gesamte diagnostische Röntgentechnik gültig wäre, diese Betrachtungsweise nicht geeignet ist. An Stelle der absoluten Grössen und Zusammenhänge soll man die Zusammenhänge der relativen Änderungen von sämtlichen Grössen suchen, die in der Röntgentechnik vorkommen und massgebend für die Bildgestaltung sind. Das heisst, man soll die in der Röntgentechnik objektiv bestehenden Zusammenhänge beschreiben und dabei sämtliche subjektive Urteile ausschalten. Wir werden die Parameter der Röntgentechnik als relativ veränderte Grössen darstellen, in zwei Gruppen anordnen und diejenige Gleichung

$$f_1\left(\frac{\Delta x_1}{x_1}, \frac{\Delta x_2}{x_2}, \ldots, \frac{\Delta x_k}{x_k}\right) = f_2\left(\frac{\Delta x_{k+1}}{x_{k+1}}, \ldots, \frac{\Delta x_n}{x_n}\right) \qquad (2)$$

suchen, die ein Gleichgewicht der relativen Änderungen darstellt, wobei $\frac{\Delta x_1}{x_1}, \frac{\Delta x_2}{x_2}, \ldots, \frac{\Delta x_k}{x_k}, \ldots, \frac{\Delta x_n}{x_n}$ die relativen Änderungen der $x_1, \ldots, x_k, \ldots, x_n$

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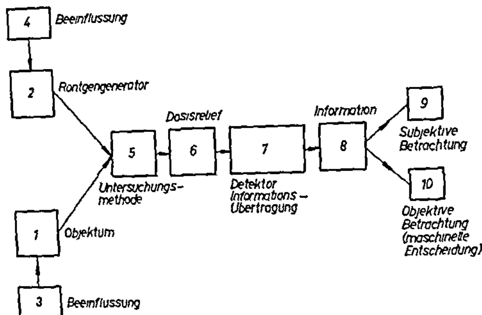


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Grössen bedeuten. Dadurch wird die Bestrebung auf die Bestimmung der Struktur, auf die Erforschung der objektiven inneren Zusammenhänge gerichtet.

Unter den bereits früher erwähnten Parametern der Röntgentechnik versteht man die Kennwerte der Aufbaukomponente des Informationsgewinnungsprozesses, wie z. B. die Röntgenröhrenspannung, der Röhrenstrom, die Belichtungszeit, usw. Die Aufbaukomponente der Informationsgewinnung sind aber die folgenden: die Röntgenstrahlen, das Objekt, usw. (Abb. 1). Unsere Bestrebung ist jetzt, den Zusammenhang, die Gesetzmässigkeiten zwischen diesen Kennwerten und das System der Beziehungen der Kennwerte innerhalb des gegebenen Prozesses zu bestimmen. Die Einheit der Kennwerte des Prozesses, ihr einheitliches System und ihr objektiver innerer Zusammenhang ist in den folgenden als die Struktur des Informationsgewinnungsprozesses bezeichnet.

Mit anderen Worten: wir können sämtliche Faktoren, die in der Röntgentechnik figurieren, in Betracht ziehen und ihre Wirkungen aufeinander und auf die Ganze in objektiver Weise bewerten. Mit Leichtigkeit können wir die Gültigkeitsgrenzen der Struktur — diejenigen Grenzen, bei welchen die quantitativen Änderungen noch nicht als qualitative Änderungen erscheinen — festlegen, sogar noch weiter gehend, wir können die Gültigkeit des Zusammenhanges (2), entsprechende approximative Zusammenhänge in Betracht ziehend, auf bestimmte Fälle der qualitativen Änderungen ausbreiten.

2. Mechanismus der Bildgestaltung (das Modell des Informationsgewinnungsprozesses) in der Röntgentechnik

Laut des Schemas der Röntgendiagnostik (siehe Abb. 1) gelangen die mit technischen Mitteln beeinflussten Röntgenstrahlen von gewünschter Qualität und Quantität (2 und 4 auf Abb. 1) mit dem entsprechend vorbereiteten Objekt, mit dem lebenden Organismus (1 und 3 auf Abb. 1) auf der *durch die Untersuchungsmethode festgelegten Weise in Wechselwirkung* (5), wodurch das Dosisrelief (6) entsteht.

Das Objekt ist meistens nicht homogen und die Strahlenintensität wird in den verschiedenen Flächenelementen der Bildebene — diese Ebene, wo die für die Bildgestaltung ausgenutzte Strahlenenergie aufgefangen wird, nennen wir folgend einfach die Bildebene — hinter dem Objekt unterschiedlich. Es besteht also die Möglichkeit, die verschiedenen Intensitätswerte durch ein Relief darzustellen, daher stammt der allgemein gebrauchte Ausdruck 'Strahlenrelief'. Auf Grund von ähnlichen Überlegungen kann hinter dem Objekt die zu jedem Flächenelement der Bildebene gehörende Dosis

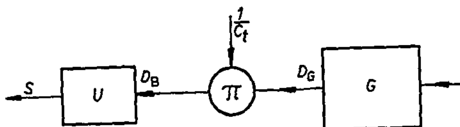


Abb 2 Vereinfachtes Schema (das Modell) der Informationsgewinnung in der Rontgentechnik

(exposure) durch ein Dosisrelief die unterschiedliche Helligkeit des Leuchtschirmes durch Helligkeitsrelief und die unterschiedliche Schwarzung des Filmes durch Schwarzungsrelief dargestellt werden

Nach der Detektierung und Informationsubertragung (7 auf Abb 1) kommt die Reihe an die subjektive (9) oder objektive (10, maschinelle Entscheidung) Betrachtung der Information (8)

Auf dem vereinfachten Schema — auf dem Modell — des jetzt erorterten Prozesses zur Informationsgewinnung (Abb 2) bedeutet D_B die Dosis welche hinter dem Objekt in einem Flachenelement der Bildebene der dort herrschenden Strahlenenergie entspricht und D_G denjenige Dosis, welche vom Rohrenbrennfleck in Einheitsabstand gemessen durch den Rontgengenerator (G) erzeugt wird und gleichzeitig fur den Generator charakteristisch ist

Der im folgenden benutzte Ausdruck Dosis' und 'Dosisleistung' entspricht der physikalischen Konzeption vom exposure und 'exposure rate' nach ICRU Wollten wir eine vollige Exaktheit bestreben musste man die Begriffe, 'Strahlenenergie und Strahlenintensitat benutzen Weil aber die Dosismessung in der Praxis ein verbreitetes Messverfahren ist, und weil in unserem Falle die Dosis (exposure) und die Dosisleistung (exposure rate) mit der Strahlenenergie und mit der Strahlenintensitat proportional betrachtet werden kann, ferner weil die theoretische Überlegungen dadurch nicht beeinflusst werden in den folgenden Betrachtungen benutzen wir weiterhin die Begriffe Dosis und Dosisleistung

C_t ist der Faktor der Wechselwirkung zwischen Objekt und Strahlung Zum Schluss stellt S (beispielsweise in der Aufnahmetechnik) die Filmschwarzung dar S bedeutet im allgemeinen die Helligkeit eines Flachenelementes im Bild welches die Information ubermittelt

Die im Vorangehenden vorkommende Grossen D_B und D_G konnen eine Dosis exposure) bedeuten aber auch eine Dosisleistung (exposure rate) z B bei Durchleuchtung oder Rontgenkinematographie Der Buchstabe π bedeutet eine Multiplikation

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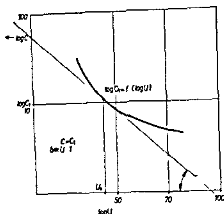


Abb 3 Änderung des Logarithmus des Objektparameters in der Funktion des Logarithmus der Röntgenröhrenspannung

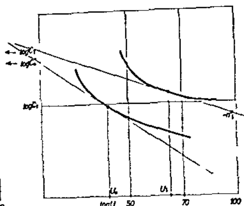


Abb 4 Funktion von $\log C_t = f$ ($\log$ U) in zwei verschiedenen Aufnahmesituationen

mittelwert welcher zum Dosisrelief des ganzen Bildes gehört womöglich klein gehalten wird (Im entgegengesetzten Falle gehört zum Dosismittelwert infolge der Nichtlinearität, nicht der Schwärzungswert gemäss der Gradationskurve sondern ein kleinerer Wert) Falls die Bildzone auf diese Weise ausgewählt wird können wir im Kenntnis der Bildzone den richtigen Schluss mit Bezug auf das ganze Bild ziehen Die richtig gewählten Zonen können als Stellen der Musterziehung betrachtet werden (siehe STIEVE 1957 WIDENMANN u Mitarb 1962)

Nach dem vorher gesagten werden in dem folgenden die relative Änderung der Dosis (exposure) des Objektparameters und der Helligkeit (Schwärzung) und der Zusammenhang dieser relativen Änderungen unter einander bestimmt

3 *Die relative Änderung der Dosis* (*exposure*)

Im Sinne des Zusammenhanges (3) ist C_t einer festgelegten röntgentechnischen Situation ausschliesslich von dem Scheitelwert der Spannung U und von ihrem zeitlichen Ablauf abhängig (In dem folgenden wird U_s einfach mit U und I_m einfach mit I bezeichnet) Also

$$C_t = f_4(U) \tag{5}$$

da (5) kontinuierlich ist und eine begrenzte Funktion aus ihr gebildet werden kann

$$\log C_t = f_5 \; (\log U) \tag{6}$$

Im allgemeinen ist also bezüglich eines Flächenelementes der Bildebene folgender Zusammenhang gültig

$$D_B \cdot C_t = D_C \tag{3}$$

wo C_t eine gut bestimmbare Zahl ohne Dimension ist, die von den Umständen der Aufnahme und von den Eigenschaften der Strahlen — auch vom Scheitelwert der Röhrenspannung und von ihrem zeitlichen Ablauf — abhängig ist.

Die Bedeutung des Zusammenhanges (3) besteht darin, dass mit seiner Hilfe der Einfluss des Röntgenapparates, D_C, der Untersuchungsbedingungen und des Objekt-Strahlung-Zusammenwirkens, C_t, der Bildgestaltung (des Detektierens D_B) und der Informationsübertragung, S, getrennt erwogen werden können.

Die Dosis (exposure), erzeugt durch Benutzung der elektrischen Energie, lautet im Sinne des gut bekannten Zusammenhanges, welches für die späteren als Grundlage dient, wie folgt

$$D_0 = b \cdot I_m \cdot U^*_s \cdot \tau \cdot \eta \cdot \varrho \cdot \xi \tag{4}$$

wobei I_m der Mittelwert des Röhrenstromes ist, U_s der Scheitelwert der Röhrenspannung, τ ist die Aufnahmezeit, η ein Faktor, die Strahlenausbeute, d. h. der Wirkungsgrad, ϱ ein Faktor, welcher den zeitlichen Ablauf des Röhrenstromes charakterisiert und auch von der Grösse abhängig ist, ξ ein Faktor der den zeitlichen Ablauf der Röhrenspannung charakterisiert, und b ist eine Konstante. Wir bemerken, dass für den Mittelwert der Dosisleistung (exposure rate) eine ähnliche Formel erhalten wird, worin aber die Zeit τ nicht vorkommt.

Kehren wir jetzt zum Zusammenhang (3) zurück. Im allgemeinen hat D_B in den verschiedenen Flächenelementen der Bildebene einen anderen Wert. Der Zusammenhang (3) kann aber im allgemeinen Falle bezüglich bestimmten entsprechend gewählten Zonen und im speziellen Falle — z. B. wenn das Phantom *homogen und überall von der gleichen Dicke ist* — auf das ganze Bild verallgemeinert werden. In solchem Falle braucht der Zusammenhang (3) nicht punktweise in Betracht gezogen werden, er ist nur mit Bezug auf je eine Zone des Bildes zu bewerten. Die Dosis (exposure) entspricht also in diesen Fällen dem arithmetischen Dosismittelwert des partiellen Dosisreliefs, das zur Bildzone gehört. Da zum Beispiel bei Aufnahmen die Übertragung vom Dosisrelief auf das Schwärzungsrelief, infolge der Form der Gradationskurve, nicht-linear ist, soll die *Bildzone derart* gewählt werden, dass der Mittelwert der interzonalen Dosisabweichungen bezogen auf die Zonenfläche, verglichen mit dem arithmetischen Dosis

Die relative Dosisänderung ist

$$D_r = \frac{D_{B1} - D_{B0}}{D_{B0}} \tag{13}$$

Durch Substitution von (11) und (12) wird aus (13)

$$D_r = \left(\frac{D_{G1}}{C_{t1}} - \frac{D_{G0}}{C_{t0}}\right) \frac{C_{t0}}{D_{G0}} =$$

$$= \left(\frac{D_{G1} U_1}{C_1} - \frac{D_{G0} U}{C_0}\right) \frac{C_0}{D_{G0} U_0^{n_0}} \tag{14}$$

Jetzt nehmen wir den Zusammenhang (4) in Betracht und substituieren denselben in (14)

$$D_{G1} = bI_1 U^2{}_1 \tau_1 \eta_1, \quad D_{G0} = bI_0 U^2{}_0 \tau_0 \eta_0$$

Also

$$D_r = \frac{\dfrac{bI_1 U^2{}_1 \tau_1 \eta_1 U_1}{C_1} - \dfrac{bI_0 U^2{}_0 \tau_0 \eta_0 U^{n_0}}{C_0}}{\dfrac{bI_0 U^2{}_0 \tau_0 \eta_0 U_0^{n_0}}{C_0}} =$$

$$= \frac{\dfrac{bI_1 \tau_1 \eta_1 U_1^{\quad +2}}{C_1} - \dfrac{bI_0 \tau \eta_0 U_0^{\quad +2}}{C_0}}{\dfrac{bI_0 \tau_0 \eta \, U_0^{n_0+2}}{C_0}}$$

Wenn wir weiterhin in Betracht nehmen dass

$$I_1 = I_0 + \Delta I, \; U_1 = U_0 - \Delta U \quad \tau_1 = \tau_0 + \Delta\tau \text{ ist}$$

$$\text{und } I_r = \Delta I / I_0 \quad U_r = \Delta U / U_0 \quad \tau_r = \Delta\tau / \tau_0$$

$$\text{Ferner } n_0 + 2 = \varepsilon_0 \quad n_1 + 2 = \varepsilon_1$$

dann wird

$$D_r = \frac{\dfrac{bI\,(1+I_r)[U\,(1+U_r)]^{\varepsilon_1} \tau_0 (1-\tau_r) \eta_1}{C_1} - \dfrac{bI_0 U_0^{\varepsilon_0} \tau_0 \eta_0}{C_0}}{\dfrac{bI_0 U^{\varepsilon_0} \tau\, \eta}{C_0}}$$

Funktion und auch ihr Differentialquotient

$$\frac{d \log C_t}{d \log U} = -n\,(\log U) \tag{7}$$

wo n die Richtungstangente der Berührungslinie der Kurve (6) bezeichnet, die ebenfalls die Funktion von log U ist (Abb. 3). Der aufgenommene Wert von (7) bei Spannung U_0

$$\left(\frac{d \log C_t}{d \log U}\right)_{U_0} = -n_0\,(\log U_0) \tag{8}$$

Die Gleichung des Geraden, konstruiert mit dem Richtungstangens (8), ist

$$\log C_t = -n_0 \log U + \log C \tag{9}$$

Die Einführung der logarithmischen Funktion (6) war deshalb notwendig, weil die Richtungstangente n, welche mit ihrer Hilfe bestimmt wurde, einen einfachen, zweckentsprechenden Ausdruck von C_t ermöglicht. Auf Grund von (9) wird nämlich die Spannung U_0 folgendermassen gestaltet

$$C_t = \frac{C}{U_0} \tag{10}$$

Nehmen wir jetzt als Grundlage, zwei röntgentechnische Situationen, z. B. zwei Aufnahmen. Bei der ersten wird die Aufnahme mit U_0 Spannung, I_0 Röhrenstrom, τ_0 Aufnahmezeit, η_0 Röhrenwirkungsgrad gemacht. (Einfachheitshalber werden jetzt die Faktoren ϱ und ξ vernachlässigt und b konstant genommen; aus dem weiteren ist es leicht einzusehen, dass es keine Schwierigkeit bereitet, sie in Betracht zu ziehen.) Der Objektparameter (Abb. 4) ist

$$C_{t\,0} = \frac{C_0}{U_0^n} \tag{11}$$

Bei der zweiten Aufnahmesituation wird die Aufnahme mit U_1 Spannung, I_1 Röhrenstrom, τ_1 Aufnahmezeit, η_1 Röhrenwirkungsgrad gemacht und der Parameter des Objektes ist

$$C_{t\,1} = \frac{C_1}{U_1} \tag{12}$$

Die relative Dosisanderung ist

$$D_r = \frac{D_{B\,1} - D_{B\,0}}{D_{B\,0}} \tag{13}$$

Durch Substitution von (11) und (12) wird aus (13)

$$D_r = \left(\frac{D_{G\,1}}{C_{t\,1}} - \frac{D_{G\,0}}{C_{t\,0}}\right) \frac{C_{t\,0}}{D_{G\,0}} =$$

$$= \left(\frac{D_{G\,1}\,U_1}{C_1} - \frac{D_{G\,0}\,U_0}{C_0}\right) \frac{C_0}{D_{G\,0}\,U_0} \tag{14}$$

Jetzt nehmen wir den Zusammenhang (4) in Betracht und substituieren denselben in (14)

$$D_{G\,1} = bI_1 U^{\epsilon}{}_1 \tau_1 \eta_1 \qquad D_{G\,0} = bI_0 U\ {}_0 \tau_0 \eta_0$$

Also

$$D_r = \frac{\dfrac{bI_1 U^{\epsilon}{}_1 \tau_1 \eta_1 U_1}{C_1} - \dfrac{bI_0 U\ {}_0 \tau_0 \eta_0 U_0}{C_0}}{\dfrac{bI_0 U^2{}_0 \tau_0 \eta_0 U_0}{C_0}} =$$

$$= \frac{\dfrac{bI_1 \tau_1 \eta_1 U_1\ \ {}^{+2}}{C_1} - \dfrac{bI_0 \tau_0 \eta_0 U_0\ \ {}^{+2}}{C_0}}{\dfrac{bI_0 \tau_0 \eta_0 U_0\ \ {}^{+}}{C_0}}$$

Wenn wir weiterhin in Betracht nehmen dass

$$I_1 = I_0 + \Delta I \quad U_1 = U_0 + \Delta U \quad \tau_1 = \tau_0 + \Delta\tau \text{ ist}$$

$$\text{und } I_r = \Delta I / I_0 \quad U_r = \Delta U / U_0 \quad \tau_r = \Delta\tau / \tau_0$$

$$\text{Ferner } n_0 \ + 2 = \varepsilon \quad n_1 \ + 2 = \varepsilon_1$$

dann wird

$$D = \frac{\dfrac{bI\ (1+I_r)[U_0(1+U_r)]\ {}^{1}\, \tau_0(1+\tau_r)\eta_1}{C_1} - \dfrac{bI_0 U_0\ {}^{0}\tau_0 \eta_0}{C_0}}{\dfrac{bI_0 U_0\ {}^{0}\tau_0 \eta_0}{C_0}}$$

Funktion und auch ihr Differentialquotient

$$\frac{d \log C_t}{d \log U} = -n \, (\log U) \tag{7}$$

wo n die Richtungstangente der Beruhrungslinie der Kurve (6) bezeichnet, die ebenfalls die Funktion von $\log U$ ist (Abb. 3). Der aufgenommene Wert von (7) bei Spannung U_0

$$\left(\frac{d \log C_t}{d \log U}\right)_{U_0} = -n_0 \, (\log U_0) \tag{8}$$

Die Gleichung des Geraden, konstruiert mit dem Richtungstangens (8), ist

$$\log C_t = -n_0 \log U + \log C \tag{9}$$

Die Einfuhrung der logarithmischen Funktion (6) war deshalb notwendig, weil die Richtungstangente n, welche mit ihrer Hilfe bestimmt wurde, einen einfachen, zweckentsprechenden Ausdruck von C_t ermoglicht. Auf Grund von (9) wird namlich die Spannung U_0 folgendermassen gestaltet

$$C_t = \frac{C}{U_0} \tag{10}$$

Nehmen wir jetzt als Grundlage, zwei rontgentechnische Situationen, z. B. zwei Aufnahmen. Bei der ersten wird die Aufnahme mit U_0 Spannung, I_0 Rohrenstrom, τ_0 Aufnahmezeit, η_0 Rohrenwirkungsgrad gemacht. (Einfachheitshalber werden jetzt die Faktoren ϱ und ξ vernachlassigt und l konstant genommen, aus dem weiteren ist es leicht einzusehen, dass es keine Schwierigkeit bereitet, sie in Betracht zu ziehen.) Der Objektparameter (Abb. 4) ist

$$C_{t,0} = \frac{C_0}{U_0} \tag{11}$$

Bei der zweiten Aufnahmesituation wird die Aufnahme mit U_1 Spannung, I_1 Rohrenstrom, τ_1 Aufnahmezeit, η_1 Rohrenwirkungsgrad gemacht und der Parameter des Objektes ist

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Die relative Dosisanderung ist

$$D_r = \frac{D_{B\,1} - D_{B\,0}}{D_{B\,0}} \tag{13}$$

Durch Substitution von (11) und (12) wird aus (13)

$$D_r = \left(\frac{D_{G\,1}}{C_{t\,1}} - \frac{D_{G\,0}}{C_{t\,0}}\right) \frac{C_{t\,0}}{D_{G\,0}} =$$

$$= \left(\frac{D_{G\,1}\,U_1}{C_1} - \frac{D_{G\,0}\,U}{C_0}\right) \frac{C_0}{D_{G\,0}\,U_0} \tag{14}$$

Jetzt nehmen wir den Zusammenhang (4) in Betracht und substituieren den selben in (14)

$$D_{G\,1} = bI_1U^{n}{}_1\tau_1\eta_1 \qquad D_{G\,0} = bI_0U\,{}_0\tau_0\eta_0$$

Also

$$D_r = \frac{\dfrac{bI_1U\,{}_1\tau_1\eta_1U_1}{C_1} - \dfrac{bI_0U\,{}_0\tau_0\eta_0U_0}{C_0}}{\dfrac{bI_0U^{n}{}_0\tau_0\eta_0U_0}{C_0}} =$$

$$= \frac{\dfrac{bI_1\tau_1\eta_1U_1{}^{+2}}{C_1} - \dfrac{bI_0\tau_0\eta_0U_0{}^{+2}}{C_0}}{\dfrac{bI_0\tau_0\eta_0U_0{}^{+2}}{C_0}}$$

Wenn wir weiterhin in Betracht nehmen dass

$$I_1 = I_0 + \Delta I \quad U_1 = U_0 + \Delta U \quad \tau_1 = \tau_0 + \Delta\tau \text{ ist}$$

$$\text{und } I = \Delta I/I_0 \quad U_r = \Delta U/U_0, \ \tau_r = \Delta\tau/\tau_0$$

$$\text{Ferner } n_0 + 2 = \varepsilon_0 \quad n_1 + 2 = \varepsilon_1$$

dann wird

$$D_r = \frac{\dfrac{bI\,(1+I_r)[U\,(1+U\,)]^{\varepsilon_1}\,\tau_0(1+\tau_r)\eta_1}{C_1} - \dfrac{bI_0U_0{}^{\varepsilon_0}\tau_0\eta_0}{C_0}}{\dfrac{bI_0U_0{}^{\varepsilon_0}\tau_0\eta_0}{C_0}}$$

Funktion und auch ihr Differentialquotient

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wo n die Richtungstangente der Berührungslinie der Kurve (6) bezeichnet, die ebenfalls die Funktion von $\log U$ ist (Abb. 3). Der aufgenommene Wert von (7) bei Spannung U_0

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Nehmen wir jetzt als Grundlage, zwei röntgentechnische Situationen, z. B. zwei Aufnahmen. Bei der ersten wird die Aufnahme mit U_0 Spannung, I_0 Röhrenstrom, τ_0 Aufnahmezeit, η_0 Röhrenwirkungsgrad gemacht. (Einfachheitshalber werden jetzt die Faktoren ϱ und ξ vernachlässigt und b konstant genommen, aus dem weiteren ist es leicht einzusehen, dass es keine Schwierigkeit bereitet, sie in Betracht zu ziehen.) Der Objektparameter (Abb. 4) ist

$$C_{t,0} = \frac{C_0}{U_0^n} \tag{11}$$

Bei der zweiten Aufnahmesituation wird die Aufnahme mit U_1 Spannung, I_1 Röhrenstrom, τ_1 Aufnahmezeit, η_1 Röhrenwirkungsgrad gemacht und der Parameter des Objektes ist

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$$D_r = \left(\frac{D_{G\,1}}{C_{t\,1}} - \frac{D_{G\,0}}{C_{t,0}}\right) \frac{C_{t\,0}}{D_{G\,0}} =$$

$$= \left(\frac{D_{G\,1}\,U_1^{*}}{C_1} - \frac{D_{G\,0}\,U_0}{C_0}\right) \frac{C_0}{D_{G\,0}\,U_0} \tag{14}$$

Jetzt nehmen wir den Zusammenhang (4) in Betracht und substituieren denselben in (14)

$$D_{G\,1} = bI_1U^{n}{}_1\tau_1\eta_1 \qquad D_{G\,0} = bI_0U^{n}{}_0\tau_0\eta_0$$

Also

$$D_r = \frac{\dfrac{bI_1U^{n}{}_1\tau_1\eta_1U_1}{C_1} - \dfrac{bI_0U\;{}_0\tau_0\eta_0U_0}{C_0'}}{\dfrac{bI_0U^{n}{}_0\tau_0\eta_0U_0}{C_0}} =$$

$$= \frac{\dfrac{bI_1\tau_1\eta_1U_1^{\;\;+2}}{C_1} - \dfrac{bI_0\tau_0\eta_0U_0^{\;\;+2}}{C_0}}{\dfrac{bI_0\tau\;\eta_0U_0^{\;\;+2}}{C_0}}$$

Wenn wir weiterhin in Betracht nehmen dass

$$I_1 = I_0 + \Delta I \quad U_1 = U_0 + \Delta U \quad \tau_1 = \tau_0 + \Delta\tau \text{ ist}$$

$$\text{und } I = \Delta I/I_0 \quad U_r = \Delta U/U_0,\ \tau_r = \Delta\tau/\tau_0$$

$$\text{Ferner } n_0 + 2 = \varepsilon \quad n_1 + 2 = \varepsilon_1$$

dann wird

$$D = \frac{\dfrac{bI_0(1+I_r)[U\;(1+U_r)]^{\,1}\,\tau_0(1+\tau_r)\eta_1}{C_1} - \dfrac{bI_0U\;{}^{0}\tau_0\eta_0}{C_0}}{\dfrac{bI_0U_0{}^{0}\tau_0\eta_0}{C_0}}$$

Jetzt nehmen wir an, dass $\varepsilon_1 = \varepsilon_0 + \Delta\varepsilon$, dann $n_1'' - n_0 = \Delta n = \Delta\varepsilon$ und

$$D_r = \frac{\dfrac{bI_0(1+I_r)U_0^{\varepsilon_0}(1+U_r)^{\varepsilon_0+\Delta\varepsilon}U_0^{\Delta\varepsilon}\tau_0(1+\tau_r)\eta_1}{C_1} - \dfrac{bI_0U_0^{\varepsilon_0}\tau_0\eta_0}{C_0}}{\dfrac{bI_0U_0^{\varepsilon_0}\tau_0\eta_0}{C_0'}} \tag{15}$$

— Da $(1+I_r)(1+\tau_r)$ mit $(1+Q_r)$ gleich ist, wobei

Q_r die relative Anderung der mAs bedeutet, wird also (15) nach dividieren mit $bI_0U_0^{\varepsilon_0}\tau_0\eta_0/C_0$

$$D_r = \frac{\eta_1}{\eta_0}\,\frac{C_0'(1+Q_r)(1+U_r)^{2+n\;+\Delta n}U_0^{\Delta n}}{C_1'} - 1 \tag{16}$$

$$\text{oder}\quad 1+D_r = \frac{\eta_1}{\eta_0}\,\frac{(1+Q_r)(1+U_r)^{2}}{\dfrac{(1+U_r)^{-n_1}\;U_0^{-1}\,C_1}{C_0'}} \tag{17}$$

4 Die relative Änderung des Objektparameters

In dem nachstfolgenden werden wir zeigen, dass der Nenner des zweiten Teils des Zusammenhanges (17) mit der relativen Anderung des Objektparameters $C_{t\,r}$ in einfacher Weise ausgedruckt werden kann. Aus der Abb. 4 folgt

$$\log C_{t\,1} = -n_1 \log U_1 + \log C_1 \tag{18}$$

$$\text{und}\quad \log C_{t\,0}' = -n_0 \log U_0 + \log C_0 \tag{19}$$

Also

$$\log C_{t\,1}' - \log C_{t\,0} = \log(1+C_{t\,r}) =$$
$$= -n_1 \log U_1 + \log C_1 + n_0 \log U_0 - \log C_0$$

$$\text{woraus}\ (1+C_{t\,r}) = \frac{(1+U_r)^{-}\quad U_1^{\quad 1}\ C_1}{C_0}\ \text{ist} \tag{20}$$

Im Spezialfalle, z. B. bei einer Rontgenaufnahme, wird die Gradationskurve mit einer Gerade angenahert. Selbstverstandlich kann die Übertragungskurve — in diesem Falle die Gradationskurve — auch anders approximiert werden. Dann erhalten wir bezuglich der relativen Anderung der Schwarzung (Abb. 5) den folgenden Zusammenhang

$$S_r = \frac{S_1 - S_0}{S_0} = \frac{\gamma}{S_0}\log(1+D_r) \tag{21}$$

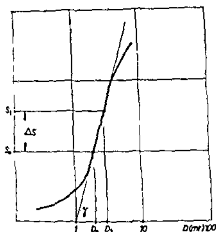


Abb. 5. Filmschwärzungskurve und deren Annäherung mit einem Geraden

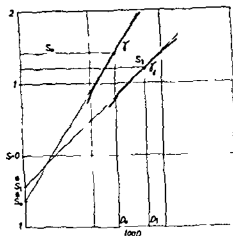


Abb. 6. Annäherung der Gradationskurven zur Bestimmung der Grundgleichung der Röntgenaufnahmetechnik

wo S_0 die zur Dosis (exposure) D_0 gehörende Schwärzung und γ die Richtungstangente der Gradationskurve bedeutet. Durch Substitution der Zusammenhänge (17) und (20) in (21) erhalten wir einen grundlegenden Zusammenhang der allgemeinen Theorie in der Röntgenaufnahmetechnik bezüglich der relativen Schwärzungsänderung

$$S_r = \frac{\gamma}{S_0} \log \frac{\eta_1}{\eta_0} \frac{(1+U_r)(1+Q_r)}{(1+C_{tr})} \tag{22}$$

Falls die Übertragungskurve bezüglich der relativen Änderungen mit Geraden approximiert wird und a (im Falle von $S_0 = 1$ und $\gamma = 1$) die Richtungstangente der Gerade bedeutet, so wird

$$S_r \cong \frac{\gamma}{S_0} a \left[\frac{\eta_1}{\eta_0} \frac{(1+U_r)(1+Q_r)}{(1+C_t)} - 1\right] \tag{23}$$

In den obigen Zusammenhängen wird im allgemeinen

$$C_{tr} = \frac{(1+U)^{-} \quad U_0^{-4} C_1}{C_0} - 1 \tag{24}$$

und falls $\Delta n \to 0$, $n_1 \approx n_0 \approx n$, dann wird

$$C_{tr} = \frac{(1+U_r) \quad C_1}{C_0} - 1 \tag{25}$$

Jetzt nehmen wir an, dass $\varepsilon_1 = \varepsilon_0 + \Delta\varepsilon$, dann $n_1{}' - n_0{}' = \Delta n = \Delta\varepsilon$ und

$$D_r = \frac{\dfrac{bI_0(1+I_r)U_0{}^{\varepsilon_0}(1+U_r)^{\varepsilon_0+\Delta\varepsilon}U_0{}^{\Delta\varepsilon}\tau_0(1+\tau_r)\eta_1}{C_1} - \dfrac{bI_0U_0{}^{\varepsilon_0}\tau_0\eta_0}{C_0}}{\dfrac{bI_0U_0{}^{\varepsilon_0}\tau_0\eta_0}{C_0}} \tag{15}$$

— Da $(1+I_r)(1+\tau_r)$ mit $(1+Q_r)$ gleich ist, wobei

Q_r die relative Änderung der mAs bedeutet, wird also (15) nach dividieren mit $bI_0U_0{}^{\varepsilon_0}\tau_0\eta_0/C_0$

$$D_r = \frac{\eta_1}{\eta_0}\,\frac{C_0\,(1+Q_r)(1+U_r)^{2+n\;+\Delta}\,U_0{}^{\Delta n}}{C_1} - 1 \tag{16}$$

$$\text{oder}\quad 1+D_r = \frac{\eta_1}{\eta_0}\,\frac{(1+Q_r)(1+U_r)^{\varepsilon}}{\dfrac{(1+U_r)^{-n}\;U_0{}^{-\Delta}\,C_1}{C_0}} \tag{17}$$

4. Die relative Änderung des Objektparameters

In dem nächstfolgenden werden wir zeigen, dass der Nenner des zweiten Teils des Zusammenhanges (17) mit der relativen Änderung des Objektparameters $C_{t\,r}$ in einfacher Weise ausgedruckt werden kann. Aus der Abb. 4 folgt

$$\log C_{t\,1} \;=\; -n_1\;\log U_1 + \log C_1 \tag{18}$$

$$\text{und}\;\;\log C_{t\,0} \;=\; -n_0\;\log U_0 + \log C_0 \tag{19}$$

Also

$$\log C_{t\,1} \;-\log C_{t\,0} \;= \log(1+C_{t\,r}) =$$
$$= -n_1\;\log U_1 + \log C_1 \;\;+ n_0\;\log U_0 - \log C_0{}'$$

$$\text{woraus}\;(1+C_{t\,r}) = \frac{(1+U_r)^{-n}\;\;U_0{}^{-\Delta n}\,C_1}{C_0}\;\text{ist} \tag{20}$$

Im Spezialfalle, z. B. bei einer Röntgenaufnahme, wird die Gradationskurve mit einer Gerade angenähert. Selbstverständlich kann die Übertragungskurve — in diesem Falle die Gradationskurve — auch anders approximiert werden. Dann erhalten wir bezüglich der relativen Änderung der Schwärzung (Abb. 5) den folgenden Zusammenhang

$$S_r = \frac{S_1 - S_0}{S_0} = \frac{\gamma}{S_0}\,\log\,(1+D_r) \tag{21}$$

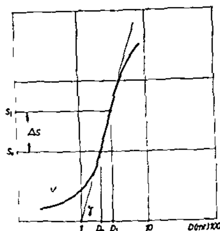


Abb. 5. Filmschwärzungskurve und deren Annäherung mit einem Geraden

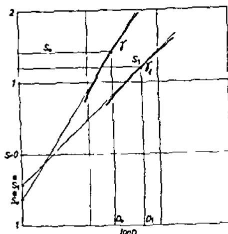


Abb. 6. Annäherung der Gradationskurven zur Bestimmung der Grundgleichung der Röntgenaufnahmetechnik

wo S_0 die zur Dosis (exposure) D_0 gehörende Schwärzung und γ die Richtungstangente der Gradationskurve bedeutet. Durch Substitution der Zusammenhänge (17) und (20) in (21) erhalten wir einen grundlegenden Zusammenhang der allgemeinen Theorie in der Röntgenaufnahmetechnik bezüglich der relativen Schwärzungsänderung

$$\boxed{S_r = \frac{\gamma}{S_0} \log \frac{\eta_1}{\eta_0} \frac{(1+U_r)(1+Q_r)}{(1+C_{tr})}} \tag{22}$$

Falls die Übertragungskurve bezüglich der relativen Änderungen mit Geraden approximiert wird und α (im Falle von $S_0 = 1$ und $\gamma = 1$) die Richtungstangente der Gerade bedeutet, so wird

$$S_r \cong \frac{\gamma}{S_0} \alpha \left[\frac{\eta_1}{\eta_0} \frac{(1+U_r)(1+Q_r)}{(1+C_{tr})} - 1\right] \tag{23}$$

In den obigen Zusammenhängen wird im allgemeinen

$$C_{tr} = \frac{(1+U)^{-} \quad U^{-\Delta} C_1}{C_0} - 1 \tag{24}$$

und falls $\Delta n \to 0$, $n \quad \approx n_0 \approx n$ dann wird

$$C_{tr} = \frac{(1+U_r)^{-} C_1}{C_0} - 1 \tag{25}$$

und zum Schluss, wenn $C_0' \approx C_1$, so wird

$$C_{t\,r} = (1+U_r)^{-n} - 1 \tag{26}$$

In praktischen Fällen ist es zweckmässig, den Ausdruck $C_{t\,r}$ die Funktion der relativen Änderungen, welche das Objekt, oder das Prüfverfahren charakterisieren (z. B. Dicke, Abstand, Raster, usw.) zu bestimmen und in (22) substituieren. (Eine nähere Auseinandersetzung werden wir ein anderesmal behandeln.)

5. *Relative Änderung von S: allgemeine Gleichung (Struktur des Systems)*

Die Zusammenhänge unserer bisherigen Ableitungen (22) und (23) sind nur in beschränktem Masse gültig, da sie die relativen Änderungen sämtlicher Parameter der Detektierung und der Übertragung der Information nicht in Betracht ziehen. Die spannungsabhängige Änderung der Filmempfindlichkeit wurde z. B. nicht in Betracht gezogen. Suchen wir die Struktur irgendeines Verfahrens der Röntgentechnik, so geht man folgendermassen vor: vorerst wird die relative Änderung der informationserteilenden S, als Funktion der relativen Änderung der Bilddosis (exposure)

$$S_r = f_6\,(D_{B\,r})$$

dann substituieren wir die bereits bekannte Funktion

$$D_{B\,r} = f_7\,(C_{t\,r},\, D_{G\,r})$$

in diesem Zusammenhang. Die Struktur des Systems, d. h. die Gleichung des röntgentechnischen Verfahrens wird so gewonnen, wenn wir $S_r = 0$ machen.

Das bisher Gesagte demonstrieren wir in Bezug auf die Röntgenaufnahmetechnik. Zur Bestimmung der relativen Änderung der Schwärzung haben wir zweierlei Schwärzungskurven aufgenommen (Abb. 6). In dem ersten Falle soll zur Dosis D_0 die Schwärzung S_0 und die Gamma der Gradationskurve γ_0 sein. In diesem Falle wird

$$S_0 = \gamma_0 \log D_0 + S_0^* \tag{27}$$

In anderem Falle

$$S_1 = \gamma_1 \log D_1 + S_1^* \text{ wird} \tag{28}$$

Die relative Änderung der Schwärzung wird also

$$S_r = \frac{\gamma_1 \log(D_0+\Delta D) - \gamma_0 \log D_0 + S_1^* - S_0^*}{\gamma_0 \log D_0 + S_0^*} \tag{29}$$

Die Gleichung der Aufnahme Anfertigung wird nun so erhalten dass in (29) $S_r = 0$ substituiert wird

$$\boxed{\Delta_1 \log D_0 + \Delta S^* + \gamma_1 \log (1+D_r) = 0} \qquad (30)$$

oder umgeordnet und den Zusammenhang (22) substituierend, zum Schluss

$$\frac{\gamma_r}{1+\gamma_r} \log D_0 + \frac{\Delta S^*}{\gamma_0(1+\gamma_r)} = - \log \frac{\eta_1}{\eta_0} \frac{(1+U_r)\ (1+Q_r)}{(1+C_{t\,r})} \qquad (31)$$

Da in (31) samtliche Faktoren zur Anfertigung der Aufnahme vorhanden sind konnen wir sie als die allgemeine Gleichung der Aufnahme Anfertigung betrachten

Zum Schluss bemerken wir dass die Struktur im Falle der Rontgendurchleuchtung sehr einfach wird da in diesem Falle, infolge der Linearitat der Detektierung und der Übertragung

$$(1+C_{t\,r}) = \frac{\eta_1}{\eta_0}(1+U_r)^{*}(1+I_r) \quad \text{wird}$$

ZUSAMMENFASSUNG

Das Hauptziel der Rontgentechnik ist die Informationsgewinnung Mit Kenntnis der Aufbaukomponente des Informationsgewinnungsprozesses kann ein vereinfachtes Modell fur die Rontgentechnik aufgestellt werden Mit Hilfe dieses Modells konnen alle Einzelfaktoren graphisch dargestellt und mathematisch formuliert werden mit anderen Worten die Struktur des Informationsgewinnungsprozesses erkannt und festgelegt werden

SUMMARY

The main aim of roentgenography is to obtain information With knowledge of the constitutional elements in the information retrieval process a simplified model for roentgen techniques may be set up With the aid of this model *the characteristic relationships* may be accounted for graphically and mathematically expressed in formulas which describe the structure of the information retrieval *process*

RÉSUMÉ

Le but principal de la technique radiologique *est l obtention* d information Connaissant les composants constitutifs du processus d obtention d information on peut établir un modèle simplifié pour la technique radiologique *Grâce* à ce modèle on peut déterminer les rélations caractéristiques par des méthodes graphiques et exprimer leurs rapports en formules mathématiques en d autres termes la *structure* du processus d obtention de l information

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